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ORIGINAL PAPER

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Application of GRAM and TLD to the resolution and quantitation of real complex multicomponent mixtures by fluorescence spectroscopy

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Abstract The application of the generalised rank annihilation method (GRAM) and the trilinear decomposition (TLD) method to the resolution and quantitation of fluorescence excitation–emission matrices of a ternary mixture of pesticides, carbendazim, fuberidazole, and thiabendazole, with overlapped spectra is described. The results obtained with both methods are compared and evaluated using measures of similarity (correlation coefficients) between the real and estimated spectra. Both approaches have been tested using augmented data matrices containing only two samples, but none of these methods succeeded completely in resolution of the system. When TLD was applied to augmented data matrices containing more than two samples better performance was achieved. To illustrate the application of both algorithms to real samples, they were used in the analysis of water samples containing the target pesticides. Again, TLD had an advantage over GRAM because the ability to analyse data from multiple (more than two) samples simultaneously allowed the resolution of the mixtures.

Keywords Three-way analysis · GRAM · TLD · Fluorescence excitation emission matrix · Pesticides

Introduction

Nowadays, analytical chemistry laboratories have instrumentation capable of providing second order tensors or two-dimensional matrices of data for each sample [1], which usually has a beneficial effect on analytical capability [2]. Typical examples are the excitation–emission matrices obtained in molecular fluorescence [3, 4, 5], as well as the data matrices generated in hyphenated chromatographic systems [6, 7], such as liquid chromatography (LC) with diode-array detection (DAD), gas chromatography (GC) with mass spectrometric detection (MS) or two-dimensional GC. The utility of these high-order tensors of data for the simultaneous determination of several analytes in unknown samples has been established in the literature [8, 9].

Multivariate data analysis methods are very suitable to handle this type of data providing quantitative and/or qualitative information, especially for those cases where full selectivity cannot be achieved and traditional univariate data analysis methods fail. In particular, self-modelling curve resolution methods [10] allow to resolution of data in terms of the true response profiles of the components and their concentrations (contributions) in the original data matrix without a priori knowledge about the system. In the case of fluorescence spectroscopy, multivariate curve resolution (MCR) allows determination of the excitation and emission spectra of target analytes and their contribution without using reference spectra, i.e. no calibration set is needed as in one-way multivariate analysis.

Approaches for curve resolution can be classified in two categories:

1. those that use a single data matrix in the analysis, i.e. two dimensional data, which can provide rich qualitative information but cannot provide quantitative information and
2. those that use multiple samples in the analysis, i.e. three way data, which allow solution of ambiguities present in the analysis of two-way data [10].

Methods such as iterative target factor analysis (ITTFA) [11], evolving factor analysis (EFA) [12, 13, 14], simple to use interactive self-modelling mixture analysis (SIMPLISMA) [15], orthogonal projection approach (OPA) [16, 17] or heuristic evolving latent projection (HELP) [18, 19, 20] belong to the first category. On the contrary, approaches such as the generalised rank annihilation method (GRAM) [21, 22, 23, 24], trilinear decomposition (TLD) method [3, 25, 26, 27], parallel factor analysis (PARAFAC) [5, 28, 29]

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or the extension of the alternating least squares (ALS) [4, 30, 31] to three way data are representatives of the second category.

Three-way resolution methods, working with trilinear data [1], show a significant improvement in the estimation of the true response profiles with the additional advantage of providing quantitative information, even in the presence of unknown interferences. Two groups can be distinguished within three-way MCR:

1. those based on non-iterative procedures and
2. those based on the application of iterative methods focused on the optimisation of initial estimates.

GRAM and TLD are good representatives of the former group and PARAFAC and MCR-ALS of the latter.

As said above, GRAM and TLD require trilinear data (i.e. every compound must be defined by the same spectral and concentration profiles in the different appended data matrices), and do not need initial estimates. GRAM needs only a single calibration sample, and it works by building a joint model for the calibration and prediction sample data matrices. An important advantage of this joint model is that correct predictions of target analytes are feasible without modelling the interferences. On the other hand, TLD is an extension of GRAM where multiple standards rather than a single sample are used.

In this work the applicability of high-order data analysis techniques, such as GRAM and TLD, to fluorescence spectroscopy data has been evaluated. Both methods have been applied to a ternary pesticide mixture with overlapped signals in both excitation and emission domains, and their ability in the resolution of such fluorimetric data has been discussed.

Theory

Fluorescence spectroscopy instruments provide for each run a bilinear data matrix $R_{(m\,n)}$ that can be expressed as the product of two matrices, $X_{(m\,c)}$ containing the individual excitation spectra, and $Y_{(n\,c)}$ containing the individual emission spectra, where m and n represent the emission and excitation spectra registered, and c the number of chemical species. The corresponding bilinear model can be written as:

$$R_{(m\,n)} = X_{(m\,c)} Y^{T}_{(n\,c)} + E_{(m\,n)} \quad (1)$$

where $E_{(m\,n)}$represents the residual error.

In the field of fluorescence spectroscopy the instrumental response is linearly dependent on concentration, and in consequence the data follows the trilinear model:

$$R_{(m\,n)} = X_{(m\,c)} Y^{T}_{(n\,c)} Z_{(r\,c)} + E_{(m\,n)} \quad (2)$$

where Z is the matrix containing the quantitative (relative) information and r the spectrofluorimetric run (or number of stacked matrices).

The principal advantage of trilinear over bilinear models is that the former result in an unique emission and excitation profile for each analyte in every run, while profiles extracted by the latter have rotational ambiguity. In both cases, there is ambiguity of scale, because the absolute magnitude of individual profiles is not determined without additional information. However, this does not impede their use to quantitative measurements as long as an adequate reference scale is selected. Here, the profiles obtained are normalised to a convenient scale (unit scale) with the aim of performing the qualitative interpretation of the profiles.

GRAM and TLD algorithms

A detailed description of GRAM and TLD has been given elsewhere [21, 22, 25]. Here, only a brief description of each method is performed.

GRAM uses the bilinear data structure from the excitation–emission matrix of a sample M and a calibration standard N to resolve and quantify targeted unresolved peaks by a mathematical algorithm that involves two main steps. In the first step, the addition matrix is decomposed by singular value decomposition (SVD) obtaining orthogonal factors (scores and loadings). The rank of the addition matrix ideally corresponds to the number of different chemical species in M and N. In the second step, an eigenvalue problem for a matrix made from the decomposition products and the N matrix is solved. The outcome is a transformation matrix that converts the results of the SVD step into meaningful information, i.e. pure profiles along each dimension. So, the cross product of the two estimated profiles for each analyte allows reconstruction of the analyte's profile resolved and normalised to unit scale.

TLD can be presented as an extension of GRAM where multiple standards are used, which leads to reach better prediction ability. The working procedure can be summarised as follows:

1. application of SVD to the row-wise, column-wise and tube-wise unfolded matrices from the original tensor obtaining the row space scores (U), the column space scores (V) and the first two vectors of the tube space scores (W);
2. determination of two representative pseudosamples, G_1 and G_2, by projection of the original tensor on the (U,V,W) basis sets; and
3. determination of X and Y matrices from the resolution of the generalised eigenvalue/eigenvector problem for matrices G_1 and G_2, and estimation of Z by least squares (given X and Y).

GRAM and TLD algorithms have been performed using Wise's Toolbox [32].

Experimental

Instrumental analysis

The data were acquired on an Aminco–Bowman Series 2-luminescence spectrometer (SLM Aminco, Rochester, NY, USA) equipped with a 150 W continuous Xenon lamp. The instrument was inter-

faced by a GPIB card and driven with a PC Novo Pentium microcomputer provided with the AB2 software version 1.40, running under OS/2 2.0, for spectral acquisition. For acquisition of three-dimensional excitation–emission spectra the scan rate of the monochromators was maintained at 7 nm s^{-1}. The data matrices were collected in a reduced domain, from 310 to 370 nm in emission domain and from 260 to 306 nm in excitation domain, in order to avoid the overlapping between the interference of the Rayleigh scattering and the analyte signals. All measurements were performed in a 10 mm quartz cell at 750 V.

A Büchi Vac V-500 (Switzerland) vacuum system connected to a Waters (Milford, MA, USA) extraction manifold was used as a water preconcentration system.

Chemicals and solvents

Analytical standards (Pestanal quality) of carbendazim (methylbenzimidazol-2-ylcarbamate), fuberidazole (2-(2-furyl) benzimidazole), and thiabendazole (2-(thiazol-4-yl) benzimidazole) were obtained from Riedel–de Haën (Seelze, Germany). Stock solutions of the fungicides were prepared by dissolving the reagent (99% purity) in methanol (HPLC grade) from Panreac (Barcelona-Spain) at a concentration of 200 μg mL^{-1}. This solution was stored in dark glass bottles at 4 °C. The working solutions, at 1 μg mL^{-1} for carbendazim and thiabendazole and at 0.01 μg mL^{-1} for fuberidazole, were prepared by dilution with methanol.

Table 1 Concentration of data set matrices in μg L^{-1}

Data matrices	Compound		
	Carbendazim	Fuberidazole	Thiabendazole
S_1	50	–	–
S_2	–	0.7	–
S_3	–	–	35
S_4	60	0.5	20
S_5	50	0.8	5
S_6	60	0.2	30
S_7	10 [a]	0.4	4
S_8	50	0.8	2.5 [a]
S_9	20	0.4	4
R_1	30	0.3	30
R_2	20	0.1 [a]	25
R_3	80	0.5	5
R_4	50	0.8	25

[a]Quantification limit

Fig. 1 Illustration of the bilinear structure in the excitation–emission data matrices from fluorescence spectroscopy of a mixture of pesticides: (*1*) carbendazim, (*2*) fuberidazole, (*3*) thiabendazole

Solid-phase extraction (SPE) was carried out using a cartridge containing 0.5 g of C_{18} stationary phase from Waters.

Data analysis

Nine data sets, S_1, S_2, S_3, S_4, S_5, S_6, S_7, S_8, S_9, corresponding to individual compounds or mixtures of them at different concentrations levels were obtained. All of them had dimensions 50×38, where the number of rows (50) is equal to the number of emission spectra and the number of columns (38) is equal to the number of excitation spectra. S_1, S_2 and S_3 represented the individual data matrices, at high concentration levels for carbendazim, fuberidazole and thiabendazole respectively. S_4–S_9 represented mixtures of the three pesticides at different concentration levels. Table 1 shows these concentration values.

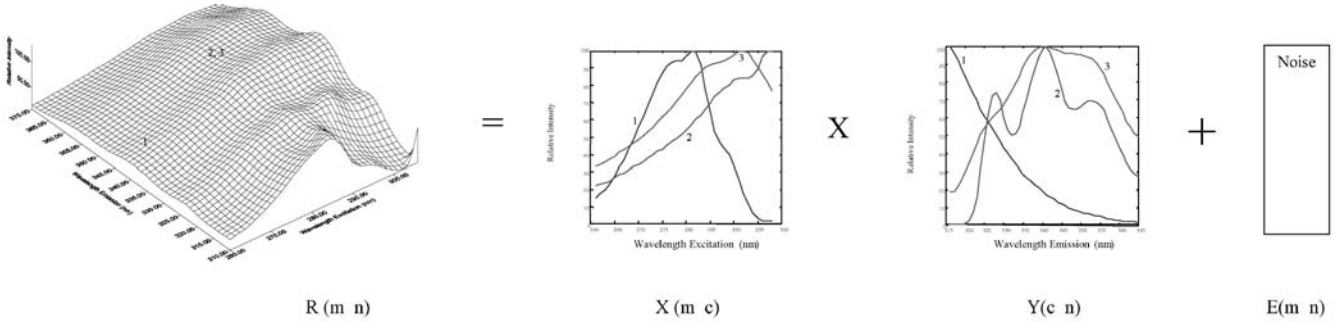
On the other hand, four data sets (Table 1), R_1 to R_4, corresponding to mixtures of the three compounds after extraction from water samples using C_{18} cartridges [33] were obtained.

The three individual and mixture data matrices were arranged in augmented data matrices. The augmented row-wise data matrix was obtained by setting each of the data matrices at the side of the other and keeping in common their rows order (emission spectra), i.e. an augmented matrix with two samples had dimensions 50×76.

Results and discussion

The performance of GRAM and TLD methods was tested on a pesticide ternary mixture in fluorescence spectroscopy. GRAM and TLD allow decomposition of the excitation–emission matrix with bilinear structure into the useful information presented in Fig. 1. In this way the bilinear part of the data matrix is modelled as the product of two matrices, each one containing the pure spectral profile vectors for the target pesticides on a given column. The non-bilinear part of the data matrix is grouped into one matrix named as noise. The data matrix corresponding to a pesticide mixture presented in the Fig. 1, in the form of a surface plot, depicts the overlapped signals of the three compounds, and especially for fuberidazole and thiabendazole both in the emission and excitation domains.

The validation of the spectral profiles of carbendazim, fuberidazole and thiabendazole recovered by GRAM and TLD was carried out by comparison with the pure spectra of the compounds obtained by analysing standards. The estimation of the similarity between the pure or real and the recovered spectra of each pesticide was performed by calculation of the correlation coefficient as the cosine of the angle between these two spectral vectors. Correlation values of 1, or close to 1, indicate very similar shapes for



both spectra, while lower correlation values mean that pure and recovered profiles are different.

Both algorithms were tested in the emission and excitation domains, but slightly better correlation coefficients were obtained in the emission domain.

Application of GRAM and TLD to the resolution of standard mixtures of the target pesticides

The number of components used in both algorithms is an important factor. According to the literature there is no agreement in this subject. Sometimes it is pointed out that the use of a smaller number of factors than the optimal number is preferred [34], while other authors indicate that to overdetermine the number of components is better than underdetermine it [25]. For the ternary mixture under study, a number of compounds from 3 to 5 was used to construct the GRAM and TLD models. No significant influence of the number of factors on the estimated spectral profiles was found. Therefore, a number of factors of 3 was used in both models.

GRAM was first applied using each one of the individual standards of the pesticides as calibration sample plus a mixture data matrix as problem sample. Excellent results were obtained in all cases with correlation values higher 0.99, except for thiabendazole in sample S_4 (Table 2). TLD provided similar results for carbendazim and fuberidazole, but poorer results were obtained for the thiabendazole pesticide with correlation values lower than 0.80.

In order to improve these results, GRAM and TLD were applied using a ternary mixture as calibration sample instead of individual standards. Now the match of the emission spectrum is good for carbendazim, but poorer matches were obtained for fuberidazole and thiabendazole, which have similar emission and excitation spectra. Table 3 summarises these results, with correlation values of 0.99 for carbendazim, that shows that the estimated profile is not dependent on which mixture sample is analysed. However, this did not occur for the predicted fuberidazole and thiabendazole profiles, more reliable predicted profiles being obtained for the more concentrated samples. It is seen in Fig. 2a that the fuberidazole profile estimated for the sample S_6, in the augmented matrix [S_4,S6], which has low fuberidazole concentration but high thiabendazole concentration, is shifted to the right and broadened. This profile showed the influence of the profile of thiabendazole. The same effect is found for the thiabendazole compound (Fig. 2b) in a sample with low pesticide concentration (S_8), in the augmented matrix [S_4,S8], and, in contrast, high fuberidazole concentration. Figure 2b shows that the estimated emission spectrum of thiabendazole is broadened to the left. In consequence, the estimated profile, both for fuberidazole and thiabendazole, is dependent of the concentration of the analysed sample by GRAM and TLD methods.

In the light of these results, TLD was applied using multiple standards as calibration samples, instead of only one data matrix (Table 3). In all cases, the model was able to differentiate between carbendazim, fuberidazole and thiabendazole, with satisfactory correlation between the estimated and real emission spectra. Now the use of the individual standards of the pesticides or ternary mixtures allowed resolution of the system. In addition, we tested that the introduction of the individual standard of carbendazim did not improve the results, and for that we decided on its elimination in order to get simpler models.

Table 2 Correlation between pure and calculated emission spectra in the analysis of data matrices using GRAM

Augmented matrix	Compound		
	Carbendazim	Fuberidazole	Thiabendazole
[S_1,S_4]	0.99	–	–
[S_2,S_4]	–	0.99	–
[S_3,S_4]	–	–	0.97
[S_1,S_5]	0.99	–	–
[S_2,S_5]	–	0.99	–
[S_3,S_5]	–	–	0.99
[S_1,S_6]	0.99	–	–
[S_2,S_6]	–	0.99	–
[S_3,S_6]	–	–	0.99
[S_1,S_7]	0.99	–	–
[S_2,S_7]	–	0.99	–
[S_3,S_7]	–	–	0.99
[S_1,S_8]	0.99	–	–
[S_2,S_8]	–	0.99	–
[S_3,S_8]	–	–	0.99
[S_1,S_9]	0.99	–	–
[S_2,S_9]	–	0.99	–
[S_3,S_9]	–	–	0.99

Table 3 Correlation between pure and calculated emission spectra in the analysis of data matrices using TLD (and GRAM) algorithms

Augmented matrix	Compound		
	Carbendazim	Fuberidazole	Thiabendazole
[S_4,S_5]	0.99(0.99)	0.98(0.96)	0.99(0.97)
[S_4,S_6]	0.99(0.99)	0.98(0.82)	0.99(0.92)
[S_4,S_7]	0.99(0.99)	0.98(0.92)	0.92(0.50)
[S_4,S_8]	0.99(0.99)	0.95(0.87)	0.91(0.90)
[S_4,S_9]	0.99(0.99)	0.91(0.86)	0.97(0.61)
[S_5,S_6]	0.99(0.99)	0.95(0.53)	0.99(0.98)
[S_7,S_8]	0.99(0.99)	0.99(0.98)	0.90(0.78)
[S_7,S_9]	0.99(0.99)	0.98(0.82)	0.78(0.97)
[S_8,S_9]	0.99(0.99)	0.99(0.88)	0.95(0.77)
[S_2,S_3,S4]	0.99	0.99	0.99
[S_2,S_3,S5]	0.99	0.98	0.99
[S_2,S_3,S6]	0.99	0.98	0.99
[S_2,S_3,S8]	0.99	0.98	0.99
[S_1,S2,S_3,S8]	0.99	0.98	0.99
[S_2,S3,S_5,S8]	0.99	0.98	0.98
[S_4,S_5,S6]	0.99	0.99	0.99
[S_7,S_8,S9]	0.99	0.99	0.99

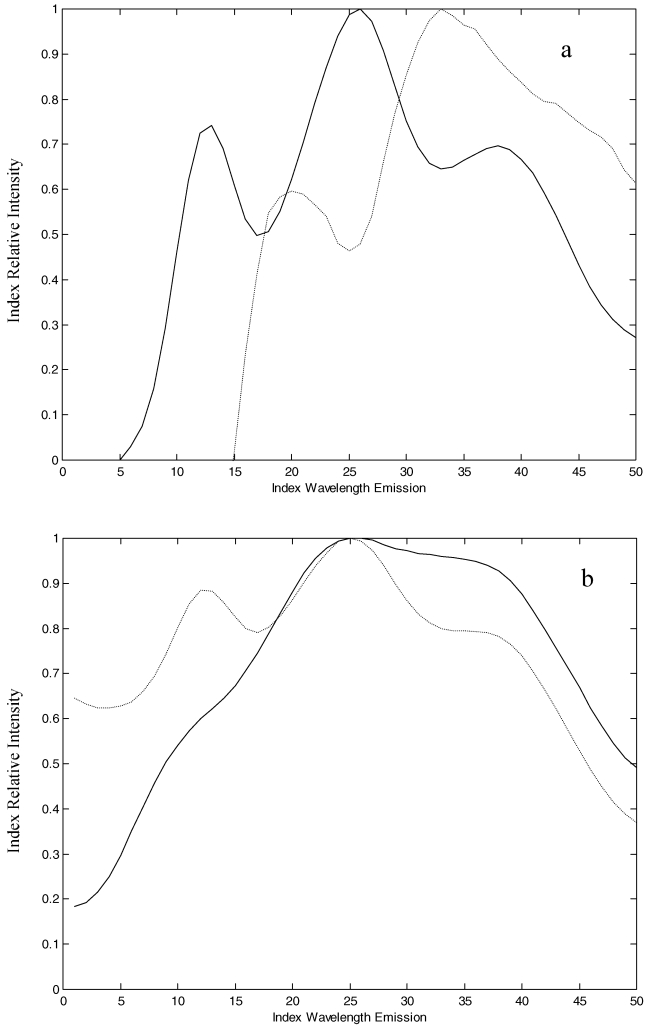


Fig. 2 Comparison of the pure emission spectra of fuberidazole and thiabendazole (*continuous lines*) with the emission spectra estimated by GRAM (*dotted lines*) for (**a**) fuberidazole in sample S_6 and (**b**) thiabendazole in sample S_8

In summary, either the inclusion of the individual standards of the components or the use of more than two ternary synthetic mixtures allowed the resolution of the system by the TLD algorithm.

Application of GRAM and TLD to the resolution of the target pesticides in real water samples

The capabilities and limitations of the GRAM and TLD algorithms in this application have been evaluated by analysis of real water samples. As in the previous part, augmented data matrices were built with two samples, each one of the standard of the components or a mixture of them plus a real sample containing a mixture of the three pesticides. Results comparable to those presented above were obtained using standard of the individual pesticides and a ternary mixture for analysis (Table 4 and Fig. 3).

Table 4 Correlation between pure and calculated emission spectra in the analysis of real water samples by GRAM

Augmented matrix	Compound		
	Carbendazim	Fuberidazole	Thiabendazole
$[S_1,R_1]$	0.99	–	–
$[S_2,R_1]$	–	0.99	–
$[S_3,R_1]$	–	–	0.98
$[S_1,R_2]$	0.99	–	–
$[S_2,R_2]$	–	0.99	–
$[S_3,R_2]$	–	–	0.99
$[S_1,R_3]$	0.99	–	–
$[S_2,R_3]$	–	0.98	–
$[S_3,R_3]$	–	–	0.95
$[S_1,R_4]$	0.99	–	–
$[S_2,R_4]$	–	0.96	–
$[S_4,R_1]$	0.99	0.89	0.86
$[S_4,R_2]$	0.99	0.66	0.84
$[S_4,R_3]$	0.99	0.90	0.79
$[S_4,R_4]$	0.99	0.93	0.80
$[R_1,R_2]$	0.99	0.80	0.99
$[R_1,R_3]$	0.99	0.96	0.83
$[R_1,R_4]$	0.99	0.94	0.92

Also, the use of a ternary mixture as calibration sample, instead of individual standards in GRAM, showed good correlations for carbendazim, and poorer matches for fuberidazole and thiabendazole, which were dependent on which mixture sample were estimated. In addition, slightly better results were provided with GRAM using a preconcentrated sample as calibration sample instead of a synthetic mixture.

The use of augmented matrices in TLD with more than two samples allowed to resolution of the system (Table 5). Again the presence of the individual standards of the fuberidazole and thiabendazole pesticides was crucial in order to reach good results. The use of the carbendazim standard did not provide better performance. This is in accordance with the results obtained in synthetic mixtures.

All the results presented in this section were also obtained with three factors. Here, models with from 3 to 5 factors were tried in order to know if the cartridge used to extract the pesticides from water samples added some new signal in our system. No influence of the number of factors on the estimated spectral profiles was found with the number of factors tested. In consequence the extraction step did not add any new interference in our application.

Quantitation of the analytes using GRAM and TLD algorithms

Although the TLD algorithm showed better results, both approaches were used in the quantitative determination of several data matrices (synthetic and real samples). Table 6 summarises the results obtained. Quantitative estimations

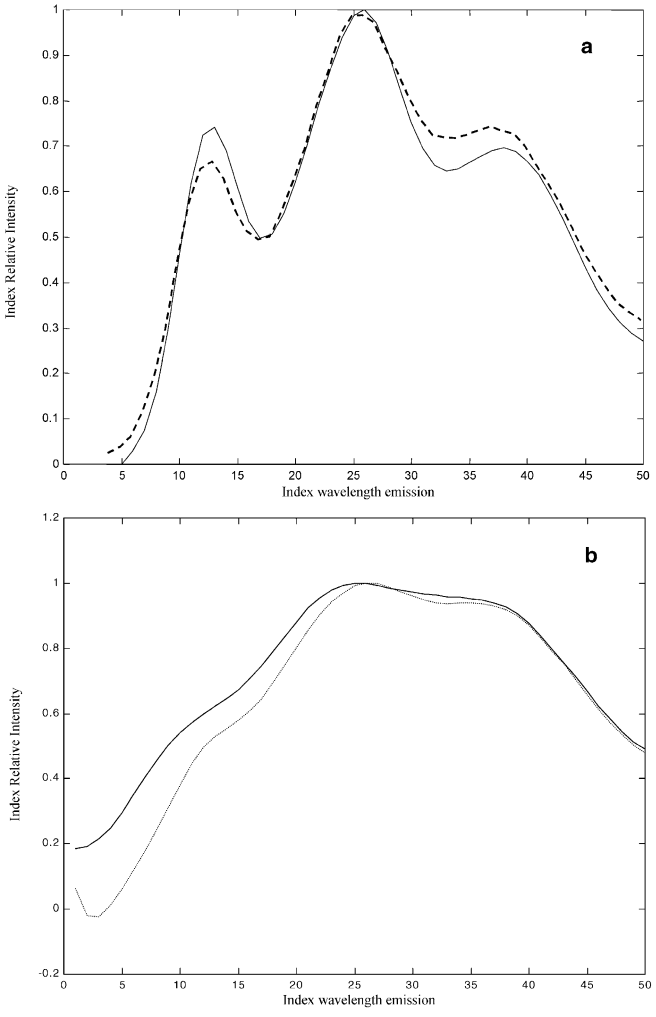


Fig. 3 Comparison of the pure emission spectra of fuberidazole and thiabendazole (*continuous lines*) with the emission spectra estimated by TLD (*dotted lines*) for: (**a**) fuberidazole in sample R_3 and (**b**) thiabendazole in sample R_4

Table 5 Correlation between pure and calculated emission spectra in the analysis of real water samples by TLD

Augmented matrix	Compound		
	Carbendazim	Fuberidazole	Thiabendazole
$[R_1,R_2]$	0.99	0.86	0.99
$[R_1,R_3]$	0.99	0.98	0.87
$[R_1,R_4]$	0.99	0.96	0.97
$[S_2,S_3,R1]$	0.99	0.97	0.99
$[S_2,S_3,R2]$	0.98	0.98	0.99
$[S_2,S_3,R3]$	0.99	0.97	0.99
$[S_2,S_3,R4]$	0.99	0.97	0.98
$[S_2,S_3,R_1,R2,R_3,R_4]$	0.99	0.97	0.99

obtained with TLD were better than the ones provided by GRAM. Again, the worst predictions were obtained for fuberidazole and thiabendazole in samples with low concentration level of these pesticides.

Table 6 Prediction (%) in synthetic and real mixtures using TLD (and GRAM) algorithms

Augmented matrix	Compounds		
	Carbendazim	Fuberidazole	Thiabendazole
$[S_4,S_5]$	108 (94)	86 (99)	95 (74)
$[S_5,S_6]$	101 (100)	85 (140)	75 (64)
$[S_7,S_8]$	109 (107)	104 (87)	98 (59)
$[S_7,S_9]$	118 (96)	104 (85)	88 (134)
$[R_1,R_2]$	72 (82)	83 (66)	111 (78)
$[R_1,R_3]$	85 (86)	103 (120)	71 (152)
$[R_1,R_4]$	79 (72)	106 (131)	84 (110)

Conclusions

Three-way data analysis by TLD showed an improvement in the estimation of the emission spectral profiles using augmented data matrices with at least three samples. The inclusion of the standards of the pesticides, specifically the introduction of the standards of fuberidazole and thiabendazole, which have more similar emission and excitation spectra, was necessary to resolve the mixture.

On the other hand, the GRAM algorithm did not show the total resolution of the system; only carbendazim was successfully determined. The application of both approaches in the analysis of real water samples showed similar results to those previously discussed for synthetic samples. In addition, TLD gave accurate quantitative results for both synthetic and real samples.

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