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Journal of Chromatography A, 1158 (2007) 184–195
JOURNAL OF CHROMATOGRAPHY A
www.elsevier.com/locate/chroma

Review

Factor analysis of hyphenated chromatographic data Exploration, resolution and quantification of multicomponent systems

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Available online 18 May 2007

Abstract

Factor analysis (FA) is a family of widely used methods to obtain the underlying sources of variation of data tables. Typically, hyphenated chromatographic data provide data tables with one elution direction and another linked to the detector response. In this context, the factors are the eluting compounds and the profiles defining each factor are the elution profile and the pure response of the compound. This article describes the use of FA in chromatography through diverse tools and problems. Examples of determination of number of compounds, peak purity problems, resolution of overlapped compounds or extension to simultaneous analysis of multiple runs (higher-order data structures) to obtain qualitative and quantitative information are reviewed.
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Keywords: Factor analysis; Curve resolution; Two-way data; Three-way data

Contents

1. Introduction

The aim of this article is the description of the applications of factor analysis (FA) to deal with chromatographic data. In the next sections, we will start with a general definition of factor analysis to realize that the underlying FA and chromatographic models are formally identical. This coincidence helps to understand the variety and wide use of FA-derived methods for analysis of chromatographic data.

Our attention will be focused first on the exploratory tools designed to determine the number of eluting components, to tackle problems of peak purity or to set elution windows. The second and most important part of this article addresses the description and applications of multivariate resolution methods, a particular family of FA-derived techniques specifically dedicated to recover the chromatographic peaks and the spectra of the components in a chromatographic run from the sole information contained in the raw response measured. This kind of methods resolves overlapped components in a run taking advantage of selective elution or spectral regions or using general information about properties of elution profiles and pure responses, the so-called constraints. Extensions of resolution techniques

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doi:10.1016/j.chroma.2007.05.045

to the simultaneous analysis of several chromatographic runs will be described that allow for resolution and quantification of multicomponent samples.

All the methodologies presented in this review will go accompanied with examples where the performance of these tools is shown and guidelines will be provided on the applicability and limitations of the most commonly used chemometric methods. Moreover, a review of the most challenging chromatographic problems solved, such as peak purity problems, quantification of analytes in natural or complex sample matrices, interpretation of high-throughput runs coming from the analysis of -omics data, process monitoring by chromatography, multidimensional or multidetection chromatography, among others, will be carried out.

2. Chromatography and factor analysis. Coincident data structure and models

A chromatographic process can be defined as the separation of a mixture of components by sequential elution. A chromatogram shows the signals collected by a detector during the elution process as a function of time. These signals (responses) can be univariate, e.g., an absorbance at a single wavelength, where the chromatogram is an array of numbers (vector), or multivariate, e.g., a full UV or MS spectrum, where the chromatogram consists of a data table (matrix), with the rows containing the full spectra collected during the elution process and the columns are the elution profiles at each channel of the response detector (see Fig. 1).

When the chromatographic data tables are formed by a series of spectra (detector responses) collected as a function of time, the underlying model has the form of the Beer–Lambert law. Let us imagine a chromatogram with two eluting compounds, represented by matrix **D.** The total raw signal will be the sum of the signals related to each one of the compounds (see Fig. 1a). Each one of these pure contributions ($\mathbf{D_i}$) can be expressed by a pure spectral profile ($\mathbf{s_i}$), which is weighted according to the concentration of the related compound along the elution direction. The column of weights or concentration values ($\mathbf{c_i}$) is actually the elution profile or chromatographic peak of the compound. Thus, the signal contribution of each eluting compound is described by a dyad of profiles, $\mathbf{c_i}$ and $\mathbf{s_i}$, which are the chromatographic peak and the related pure spectrum, respectively (see Fig. 1b). This additive model of individual contributions is equivalent to the compact representation of the bilinear chromatographic model, $\mathbf{D} = \mathbf{CS}^{\mathbf{T}}$, where the columns in matrix **C** are the elution profiles and the rows in matrix $\mathbf{S}^{\mathbf{T}}$ are their related pure spectra (see Fig. 1c).

Factor analysis encompasses a family of methods that decompose a data table into a bilinear model of factors. Each one of these factors represents a relevant source of variation of the data set. The general FA model can be expressed as $\mathbf{D} = \mathbf{F_R F_C}$ where the factor profiles in $\mathbf{F_R}$ relate to the variation in the row direction of the data and those in $\mathbf{F_C}$ to the variation in the column direc-

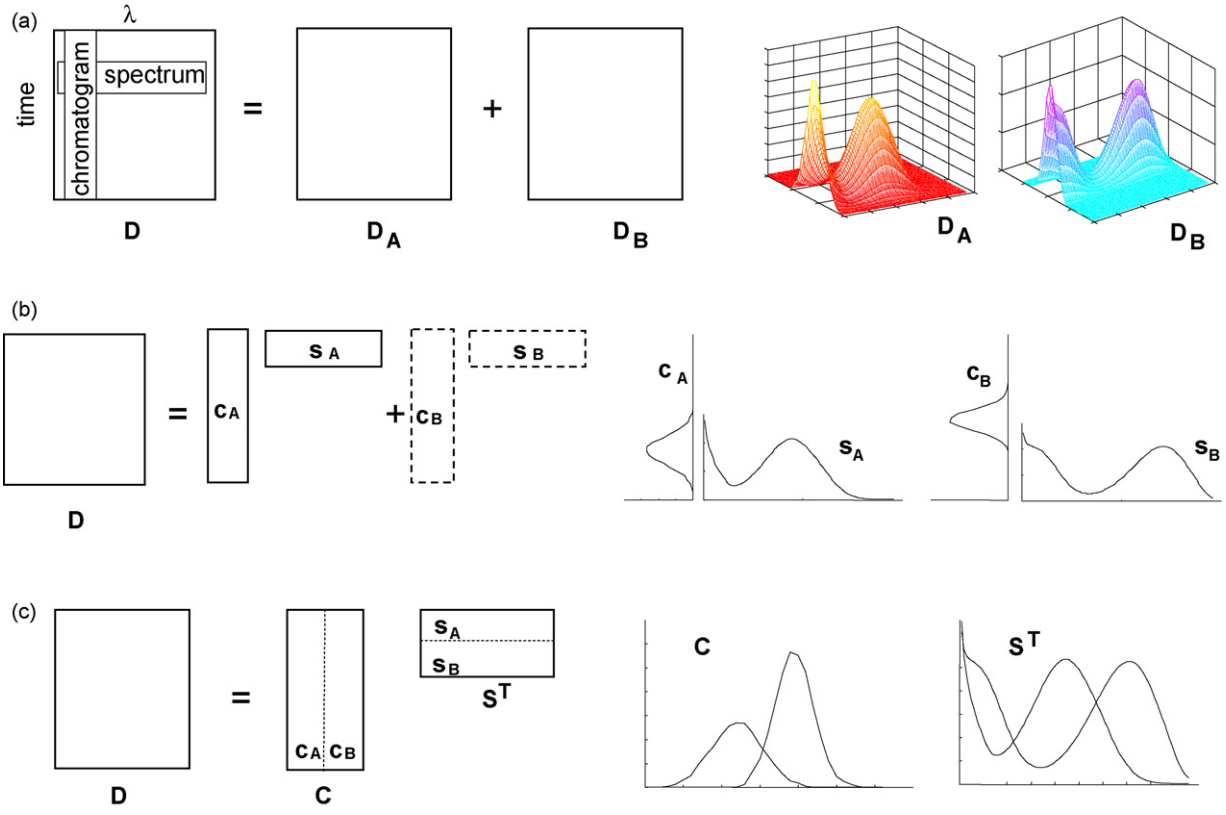

Fig. 1. The measurement model of a two-component HPLC–DAD system. (a) Described as an additive model of pure signal contributions, (b) described as a model of additive dyads of pure concentration profile and spectrum, (c) described as a bilinear model of concentration profiles and spectra.

tion. The so-called factors may have mathematical or chemical meaning depending on the method used, but the number of factors required to describe the relevant variation of a data set will remain the same. Malinowski wrote the book 'Factor analysis in Chemistry', the reference monograph that explains the use of this mathematical tool taking into consideration the structure of the chemical data [1].

As can be noticed from the descriptions above, both the chromatographic model, $\mathbf{D} = \mathbf{C}\mathbf{S}^{\mathbf{T}}$, and the general FA model, $\mathbf{D} = \mathbf{F}_{\mathbf{R}}\mathbf{F}_{\mathbf{C}}$, are bilinear. Therefore, FA-based methods will be particularly appropriate to provide information of chromatographic data sets. It is important to note that a bilinear model, formed by mathematical or by chemical factors, will detect eluting components that do have a distinct identity in terms of spectra and elution profiles. In practice, this means that two chemical compounds having identical spectra and different elution profiles would be detected and modeled as a single one, as it would happen with two compounds with different spectra and an identical elution profile. It should be stressed that compounds with very overlapped spectra or elution profiles would be detected as different, as long as the differences between their profiles are larger than the noise associated with the measured signal. Throughout the text, when we talk about eluting components, we would refer to 'observable' components, i.e., components having an elution profile and a pure spectrum different from the rest.

In the next sections, we will see that FA methods that work with mathematical factors generally provide information of exploratory value, whereas methods oriented to the recovery of chemically meaningful profiles attempt to achieve the real resolution of the chromatographic systems.

3. Exploring chromatographic data by factor analysis

Although the final goal in the analysis of a chromatographic data set is the recovery of the elution profiles and pure spectra of the compounds in the sample, a prior exploration of the data set can give valuable information that can be used afterwards into the resolution process. Exploring chromatographic data sets means estimating the number of eluting compounds (and this includes the detection of unexpected compounds, such as interferences or minor impurities), knowing how the elution sequence takes place, i.e., when compounds start and end eluting, finding selective elution or spectral ranges or locating the most relevant information in both spectral and chromatographic direction, i.e., which retention times provide the most representative spectra or which detector channels are better linked to each particular compound.

Exploration of any data table usually starts with principal component analysis (PCA), the most general tool for this purpose. Actually, the terms factor analysis and principal component analysis are often treated as synonymous in the literature, although factor analysis has a much wider meaning. PCA decomposes the data set into a bilinear model of uncorrelated mathematical factors that describe the directions of maximum variance of the data set [2,3]. These factors (principal components) are sorted in a decreasing order according to the amount of variance explained. The relevance of each factor is linked to the magnitude of a numerical value, the eigenvalue (ev) or its square root, the singular value (sv). Thus, eigenvalues linked to relevant sources of variation of the data set are large, whereas noise-related eigenvalues are small and very similar to each other. As a general rule, when we apply PCA to a chromatographic example, the number of large (significant) eigenvalues equals the number of eluting compounds in the data set. Indeed, we can reproduce any spectrum in our chromatographic run from the combination of the pure spectra of the eluting compounds, suitably weighted according to the necessary compound concentrations. These pure spectra are, therefore, the real relevant sources of variation of our data set and we have as many as eluting compounds.

Crude PCA on the complete chromatographic run can provide information on the total number of eluting compounds, expected analytes and unexpected interferences or impurities. Beyond the basic use of this tool, the generally identical size of a PCA and a chromatographic model, i.e., number of significant ev = number of eluting compounds, has been used as the central idea to design more efficient exploratory methods that take into account the specific features of a chromatographic elution. Indeed, the sequential elution of compounds in the time direction can be used to devise methods able to establish the emergence and decay of compounds by stepwise study of the chromatographic data set.

Evolving factor analysis (EFA) was the parent method conceived by Maeder et al. [4–6] to study sequential evolving processes, such as chemical reactions or elution in chromatography. Mimicking a chromatographic analysis, where the chromatogram is formed recording successive spectra as a function of time, EFA performs PCA analyses on gradually expanding data matrices in the elution direction, enlarged by adding a new spectrum (detector response) at a time. This procedure is performed from top to bottom of the data set (forward EFA) and from bottom to top (backward EFA) to investigate the emergence and the decay of the eluting compounds, respectively. Fig. 2 shows the EFA results for a four-component chromatographic data table. The overlaid forward EFA plot (thin solid lines) and backward EFA plot (thin dashed lines) are built by representing the log(eigenvalues) of each PCA analysis vs. the elution time related to the last row included in the window analysed. The lines connecting all the analogous eigenvalues (ev), i.e., all the 1st ev., the 2nd ev., the *i*th ev.,. . . indicate the evolution of the magnitude of eigenvalues along the elution process and, as a consequence, the variation linked to the eluting compounds. A new eigenvalue line seen above the noise level, marked by the pool of non-significant eigenvalues, indicates the emergence (forward EFA) or decay (backward EFA) of an eluting compound. Considering the simplest case, where components are eluting sequentially and there are no embedded peaks (i.e., peaks eluting completely under a major one), the time range between the point where the first forward EFA line and the last backward EFA line arise from noise defines the elution window (time range of compound elution) for the first eluting compound. The time range out of the elution window is the complementary zero-concentration window (time range where a compound is absent).

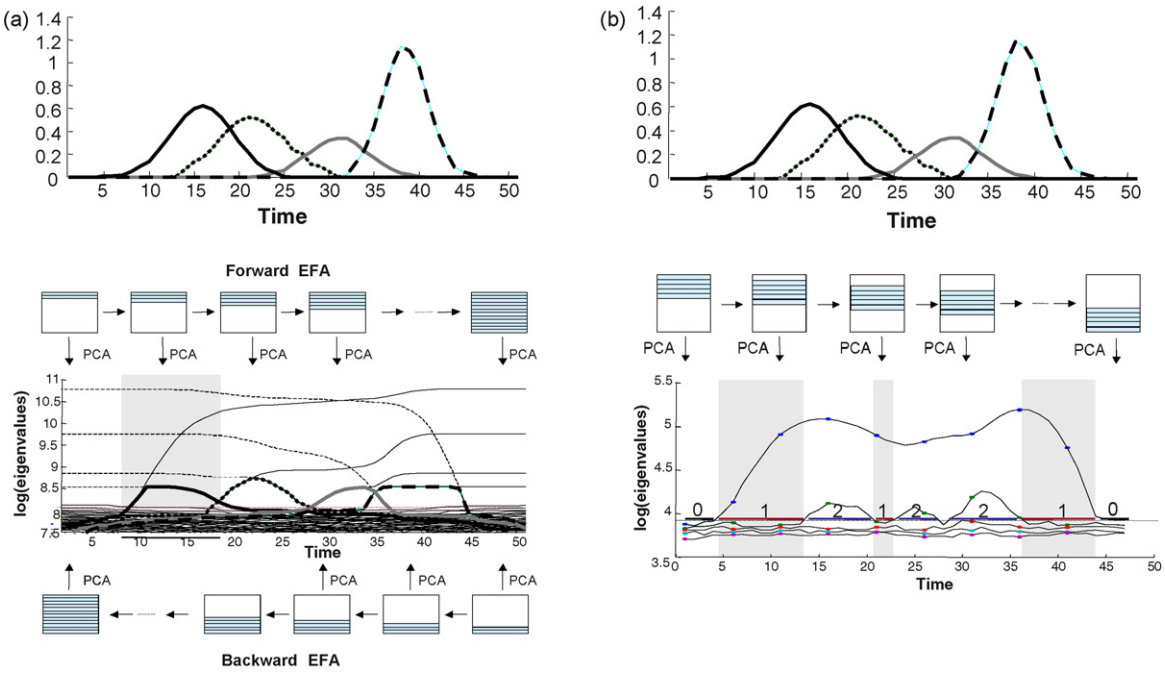

Fig. 2. (a) Top plot: concentration profiles of an HPLC–DAD data set. Bottom plot: Information derived from the data set in top plot by evolving factor analysis (EFA) scheme of PCA analyses performed. Combined forward EFA (solid black lines) and backward EFA (dashed black lines) plot. The thick lines overlaid are the derived elution profiles. The shaded zone marks the elution window for the first eluting compound. (b) Top plot: as in (a). Bottom plot: information derived from the data set in top plot by fixed size moving window-evolving factor analysis (FSMW-EFA) scheme of the PCA analyses performed. The straight lines and associated numbers mark the different windows along the data set as a function of their local rank (number). The shaded zones mark the selective windows in the data set (rank 1).

This procedure can be performed analogously for all eluting compounds in the data set [7]. The knowledge of these windows is essential for many resolution methods. Modifications of this parent method are oriented to detect the eventual presence of embedded profiles [8] and to improve the setting of the boundaries of the elution windows [9]. Still taking advantage of the sequential elution idea, connecting the first forward EFA line (marking the first emerging compound) with the last backward EFA line (marking the first decaying compound), we may obtain the approximate elution profile for the first compound. The rest of the profiles are obtained analogously connecting the *i*th forward EFA line with the *n*-*i*th backward EFA line, where *n* is the total number of eluting compounds.

Another family of methods derived from EFA performs PCA analyses on windows of fixed size that are moved along the data set. The most widely used approach of this kind is fixed size moving window-evolving factor analysis (FSMW-EFA), developed by Keller et al. [10,11]. As shown in Fig. 2b, PCA analyses are performed on fixed size windows moved row by row downwards along the elution direction of the data set. The FSMW-EFA plot shows the eigenvalues obtained in all the PCA analyses as it was done in EFA. This representation contains the information on the compound overlap in the elution direction. Thus, elution ranges where two eigenvalue lines arise from the noise level indicate the presence of two overlapped compounds. In general, the number of compounds overlapping in a certain time range equals the number of eigenvalue lines above the noise level. FSMW-EFA is particularly useful for the detection of selective elution regions for the different compounds, i.e., zones where only one compound is present. When such zones are present, obtaining the pure spectra of the related compounds is straightforward. They are thus of great help to decrease the uncertainty linked to the chromatographic resolution results. FSMW-EFA was created as a method more capable to detect impurities or minor compounds than EFA due to the local analysis of small elution windows. This sensitivity explained the widespread use of this method to address peak purity problems [10,12,13]. Modifications have appeared that adjust the size of the window to increase the capacity of detection of minor compounds and to improve the location of the boundaries of the elution regions with different compound overlap [14]. At this point, we should comment that the estimation of the number of factors or significant eigenvalues in data sets and the straightforward identification with the number of eluting compounds may present difficulties in some particular cases, when there is a strong heteroscedastic noise [15], distortions of the linear detector response [16] or non-chemical contributions to the signal, such as drift or baselines. The visual output of these eigenvalue-based methods can warn about the presence of these non-chemical artifacts and data preprocessing procedures are provided to solve many of these situations [17].

EFA, FSMW-EFA and all their derived approaches are called local rank analysis methods because they look at the chromatograms in a local fashion, with repeated analyses of restricted elution windows of the data set. Other exploratory tools look at the complete chromatographic data with the aim of locating the most representative elution times, i.e., the purest spectra, or the most representative detector channels, i.e., the purest elu-

tion profiles, in the chromatographic run. Recalling the model of real chromatographic factors, $\mathbf{D} = \mathbf{CS}^{\mathbf{T}}$, these methods seek the best approximations of either the elution profiles in **C** or the pure spectra in $\mathbf{S}^{\mathbf{T}}$ among the columns and the rows of the raw chromatographic data set, **D**, respectively. The mathematical background of these methods is very diverse [18–21]; some of them work on the bilinear model provided by PCA, such as the needle search [21] or key set factor analysis [22–24], whereas the most commonly used choose the most dissimilar rows or columns directly from the original data set, such as simple-to-use interactive self-modelling analysis (SIMPLISMA) by Windig and Guilment [25,26] or the orthogonal projection approach (OPA) [27]. Although the primary goal of all these methods is the selection of the purest profiles, all of them indirectly provide information on the number of components of the data set and have been used to address peak purity problems [19,20,28,29]. Thus, an unnecessary extra spectrum/chromatographic peak is normally discarded because either the profile selected is too similar to a previous one, or it has a clear noise pattern. Some method-specific criteria are also designed that warn about the inadequacy of the selection of a new contribution once the correct number of pure profiles has been selected [26,27]. At this point, it is worth stressing that this family of tools would yield the real profiles of a compound if there were selective spectral channels (real elution profile) and/or selective elution windows (real pure spectrum) for that particular compound. This is far from general, however, and such an assumption should never be made unless supported by complementary local rank (or other sound) information.

4. Resolving a single chromatographic run

In previous sections, we have seen repeatedly the underlying model of chromatographic measurements, i.e., $\mathbf{D} = \mathbf{CS}^{\mathbf{T}}$. Multivariate resolution methods are factor analysis tools designed to find the real underlying factors (the chromatographic profile and pure spectrum of each compound) using only the recorded chromatographic data table, i.e., they decompose the data **D** into the product $\mathbf{CS}^{\mathbf{T}}$, as shown in Fig. 1c. In contrast to previously described methods, the value of multivariate resolution lies in the fact that the recovered profiles (factors) in the bilinear model are true elution profiles and pure spectra of compounds, instead of abstract or approximate representations of them.

Lawton and Sylvestre [30] were pioneers in introducing resolution methods in chemistry in 1971. Since then, many other methods with very diverse mathematical backgrounds were proposed taking the basic ideas provided by these authors. Roughly speaking, resolution methods can be divided in non-iterative and iterative methods [31–35]. Non-iterative methods rely on the combination of small elution sections of the data set to obtain either the elution profiles or the pure spectra of the compounds. These small sections have special properties and they are built from the knowledge of the elution windows of the different components provided by exploratory methods, such as EFA or other local rank analysis methods. Once the profiles in the **C** or in the **S** matrix are recovered, the complementary matrix (**S** or **C**, respectively) is recovered through a single least-squares step [36]. Window factor analysis (WFA) by Malinowski and co-workers [37,38], subwindow factor analysis (SFA) by Manne and co-workers [39,40] and heuristic evolving latent projections (HELP) by Kvalheim and co-workers [41–43] are among the first and most significant approaches within this category. Recent algorithms are often developed from these parent approaches, such as orthogonal projection resolution (OPR) from WFA [44] or parallel vector analysis (PVA) from SFA [45]. All these methods take advantage of the sequential elution order in chromatographic data. This ordered pattern allows for setting the elution windows (a task otherwise impossible when using only local rank information) from which the small subsections of the data are built. A key point is then the correct definition of the elution windows and research has also gone in this direction [46,47] to avoid mistakes in this step that could damage the final results. Despite this critical point, an advantage of these methods is the one-at-a-time recovery of elution profiles or spectra that can make these methods useful when only partial information of a system, such as the pure spectra or the pure elution profiles of certain components, are of interest. [48,49].

Iterative resolution approaches are likely the most popular multivariate curve resolution methods due to the flexibility to cope with many kinds of data structures and chemical problems and to the ability to accommodate external information in the resolution process. All of them share a common step of optimisation (of **C** and/or **S** matrices) that starts from initial estimates of **C** or **S** that evolve in each iterative cycle to yield profiles with chemically meaningful shapes, tailored according to chemical or mathematical information included in the iterative optimisation process under the form of constraints [32–34]. The iterative optimisation ends when there is no further improvement in the profiles recovered or when the reproduction of **D** from the product $\mathbf{CS}^{\mathbf{T}}$ is satisfactory and a convergence criterion is met. Iterative target transformation factor analysis, ITTFA, developed independently by Gemperline and by Vandeginste et al. [50,51], alternating regression [52] and multivariate curve resolution-alternating least squares, MCR-ALS, by Tauler and co-workers [53–57] were the first iterative approaches proposed and still the most used, although other methodologies with different principles have subsequently appeared [58,59].

The first step in any iterative resolution method is determining the number of eluting compounds in the data set. Contrary to what could be expected, the estimation of the number of eluting compounds is not a serious problem in iterative resolution methods. If in doubt, resolution analyses with different number of components can be carried out. The analysis providing the best fit and the best chemically interpretable profiles will be adopted as the final solution. Once the number of components is known, initial estimates of either **C** or **S**, i.e., approximations of either elution profiles or spectra should be generated. The sequential elution direction of chromatographic data leads often to the use of abstract elution profiles found with evolutionary factor analysis methods, such as those found with EFA (see the exploratory section of this work) [7,13,56,57], although spectra selected by SIMPLISMA or other pure variable selection methods are also an option [26,27,60–62]. The initial estimates are the starting point in the iterative optimization.

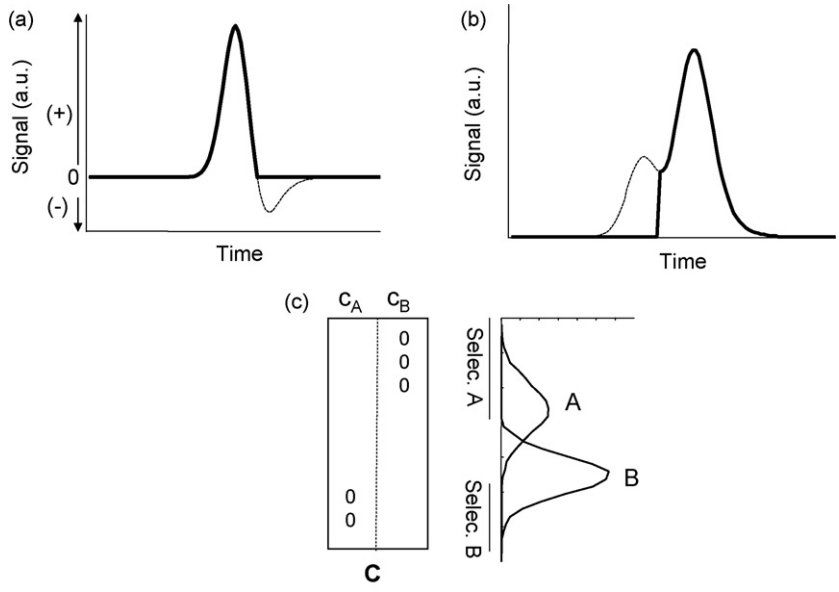

Fig. 3. Common constraints applied to chromatographic elution profiles. (a) Non-negativity, (b) unimodality. Thick profiles in (a) and (b) are constrained profiles; thin dashed lines represent elution profiles before being constrained (the non-visible part of the unconstrained profiles overlaps with the constrained profiles). (c) Selectivity, included as null concentration for the absent compounds.

The core in all iterative resolution methods is the application of constraints during the optimization of elution profiles and spectra. Constraints are chemical or mathematical properties that the concentration profiles and/or spectra should fulfill. When a profile is constrained, its shape is modified to fulfill a preselected property [30–32,54,63]. The suitable choice of constraints customizes the resolution method according to the chemical problem to be solved. Therefore, it is in the selection of constraints where the chromatographic nature of the data is taken into account. Apart from the application of non-negativity to both elution (concentration) profiles and pure spectra, as imposed to many other chemical data sets, the particular properties of the elution direction allow for the introduction of constraints related to the peak shape or to the sequential elution pattern of compounds. Thus, unimodality can be selected to preserve the presence of only one maximum in each chromatographic profile and the knowledge of the elution windows can help to set selective elution regions (time channels where only one compound elutes) or to introduce local rank information (time channels where one or several compounds are absent). Fig. 3 shows the effect of the most common constraints applied in the analysis of chromatographic data. Some constraints have appeared that try to fit the elution profile to a particular shape, defined by a mathematical function that may allow a certain asymmetry. However, these must be applied carefully and one should take into account the more or less irregular shape of the natural elution profiles, which may be very problem-dependent, before proceeding to their application [64].

All the multivariate resolution methods described above can be applied to any kind of chromatographic data, no matter the separation mechanism or the detector response used because the underlying bilinear model of the data remains the same. Thus, examples of typical hyphenated techniques, such as gas chromatography–mass spectrometry (GC–MS) [43,65–67], liquid chromatography–diode array detection (LC–DAD) [7,13,24,68] and LC–MS [69–72] can be easily found and also liquid chromatography coupled with less traditional detection systems, such as infrared, IR [73,74], nuclear magnetic resonance, NMR [75,76], Raman [77], multiwavelength fluorescence [78] and voltammetric [79] detection. Apart from the examples above, it is worth stressing situations where the power of resolution methods has helped to improve the interpretation and speed in complex chromatographic data analysis. This is the case of high-throughput chromatographic data, linked often to metabonomic or metabolomic studies, where many different compounds come into play and semiautomatic or automatic curve resolution approaches have been of great help [71,80,81].

5. Resolving several runs and other complex chromatographic data

Despite the enormous advance introduced by the use of multivariate resolution techniques in the analysis of single chromatographic runs, there are limits in the quality of the chromatographic profiles and pure spectra obtained that do not depend on the resolution method applied, but rather on the overlap among compounds in both spectral and chromatographic directions [82]. Thus, Manne provided two resolution theorems that state the conditions for a correct recovery of the elution (row) and spectra (column) profiles in the resolution of a single data set. In chromatographic terms, this would translate as follows:

(1) The correct elution profile of a compound can be recovered when all the compounds inside its elution window are also present outside (theorem 1).
(2) The correct spectrum of a compound can be recovered if its related elution window is not completely embedded inside the elution window of a different compound (theorem 2).

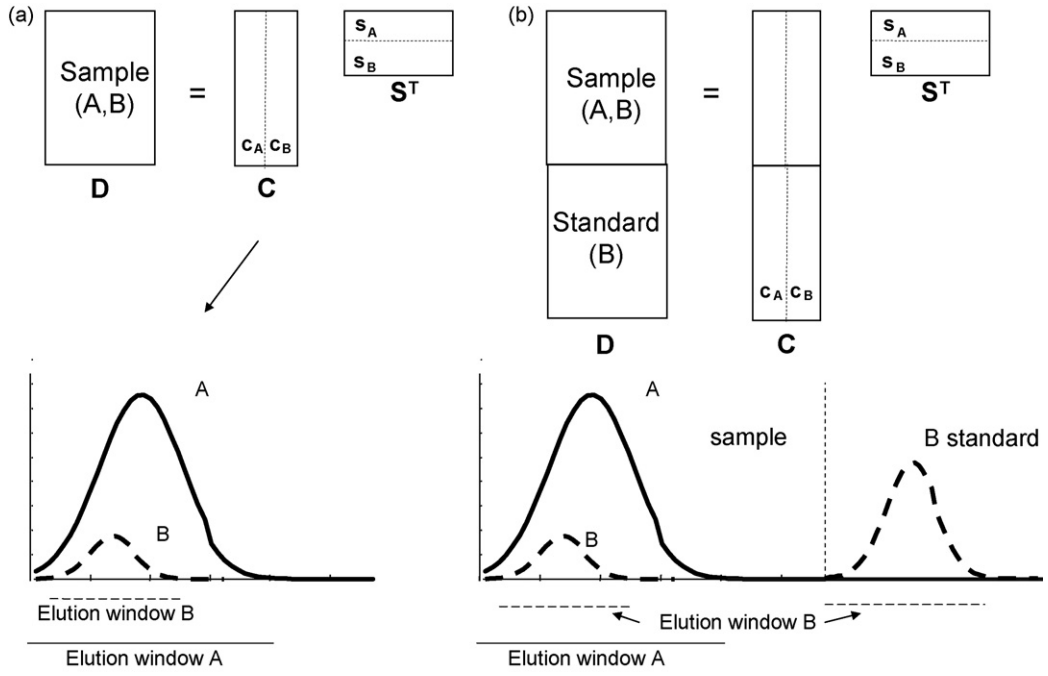

Fig. 4. (a) Elution profiles and related elution windows for a sample with a major compound (A) and an embedded minor compound (B) and for (b) the same sample with an appended B standard. The variation in the total elution window of both compounds in (b) ensures the correct recovery of elution profiles and spectra for both compounds.

It is interesting to note that, by appending additional runs in the column direction, these limitations can be largely overcome. Basically, the problem arises when we have an embedded peak under a major one. If this is the case, neither the concentration profile of the major compound (see theorem 1) nor the pure spectrum of the embedded compound (see theorem 2) can be correctly recovered. A possible way to solve this situation, but not the only one, is appending a run of a standard of the embedded compound in the column direction. Doing so, the total elution windows of both compounds fulfill the conditions for a correct resolution of their related elution profiles and spectra (see Fig. 4). Another problem that could be solved in the same manner would be related to the number of observable components. Thus, two compounds with identical elution profiles in a chromatographic run would be distinguished if an additional run with the two of them less overlapped is included in the data analysis.

Therefore, we can say that a very relevant milestone in chromatographic data analysis has been finding methods to resolve several chromatographic runs together [7,56,83,84]. There are different ways of organising chromatographic runs for simultaneous analysis (see Fig. 5). Each data arrangement demands different requirements of the data sets appended and the mathematical model that describes the measurements is also different. Thus, Fig. 5a shows several runs appended in the form of a data cube, with dimensions (retention time × wavelengths × run number). This means that all the runs should have synchronised dimensions of time and wavelength range. Whereas this is usually the case in the spectral direction, it is not necessarily so in the time direction, where several runs may have different total analysis times. Multi-way methods, such as parallel factor analysis, PARAFAC [85–87], promoted by Bro in the context of chemical problems, the generalised rank annihilation method (GRAM) [83,84,88–90] and direct trilinear decomposition (DTD) by Kowalski et al. [87,91] decompose these cubes of data into three matrices, which contain the elution profiles (**C**), the pure spectra (**S**) and quantitative information about the compounds in the different runs (**Z**). This is called a trilinear model and each compound is described by a tryad of profiles, i.e., a pure spectrum, an elution profile and a quantitative profile that contains the relative concentrations of that compound in the different runs. It is important to note that this model assumes that the elution profile of a particular compound always appears in the same location and has the same shape in all chromatographic runs. This is not often the case in real chromatographic separations. Therefore, the use of these methods is limited to very clean and reproducible chromatographic elutions and often requires data preprocessing to correct for peak shifting of the same compound among the different runs [92–95]. Nevertheless, when complex systems with severe matrix effects (natural samples) or with minor compounds come into play, these methods cannot perform adequately because the differences in peak shape and position among runs cannot be properly corrected, i.e., the trilinear model of the mathematical methods cannot describe adequately the true chromatographic behaviour. Fig. 5b and c show more flexible data arrangements and models. As can be seen, it is not necessary to build regular data cubes with the data to be analysed. The spectral direction (wavelength range) should be identical in all chromatographic runs, but the elution dimension can vary, e.g., runs with different total analysis time or different selected time regions from complete chromatograms can be analysed together. Methods such as PARAFAC2 [96–98] and MCR-ALS [32,53–56] are the ones which lead to the data

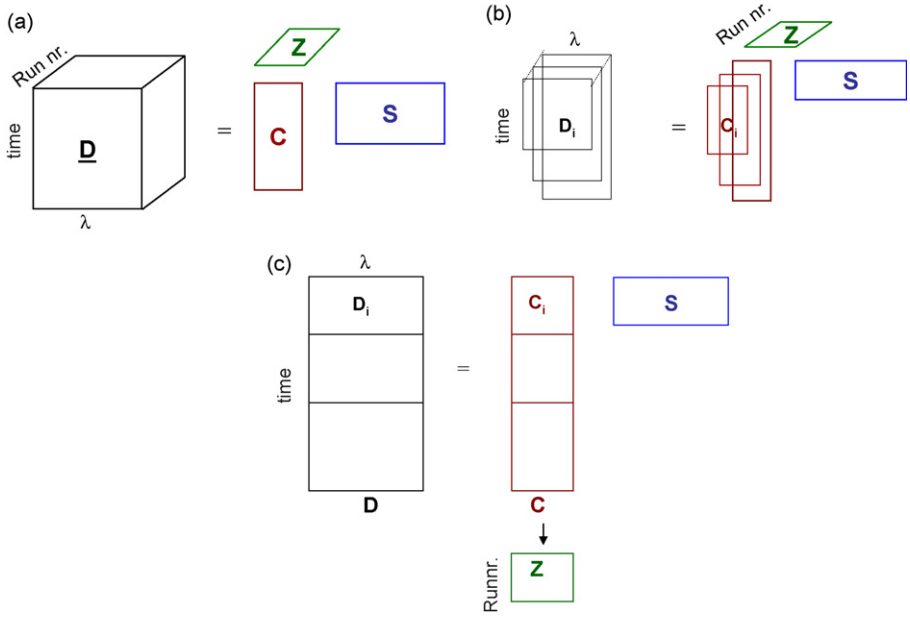

Fig. 5. (a) Data arrangement for several chromatographic runs as a data cube and decomposition into a trilinear model, with a single matrix **C** (eution profiles), **S** (pure spectra) and **Z** (quantitative information). (b) Irregular data arrangement to decompose the data in the underlying non-trilinear model of PARAFAC2. **S** and **Z** mean the same as in a) and there is a $\mathbf{C_i}$ submatrix (elution profiles) for each chromatographic run. (c) Column-wise augmented data matrix to decompose the data in the underlying non-trilinear (bilinear) model of MCR-ALS. Augmented matrix **C** contains the $\mathbf{C_i}$ submatrices of the different chromatographic runs. **Z** is derived after the data decomposition.

decompositions in Fig. 5b and c, respectively. None of these methods assumes a trilinear model; instead, a particular compound is described by a single pure spectrum (invariant for all runs) and by an elution profile per run (in each $\mathbf{C_i}$ submatrix). The fact that the elution profile of a compound could show run-to-run differences makes these methods more suitable for any kind of chromatographic system without the need for data preprocessing. Concerning the quantitative information, it can appear in a separate matrix (**Z** in Fig. 5b) or be easily derived from the augmented **C** matrix (in Fig. 5c). Because of the mathematical constraints of the method, PARAFAC2 can only handle relatively small differences in peak shape and position compared to MCR-ALS, which allows for a complete freedom in the elution profiles [99,100]. It is also important to note that, if a particular data set is really obeying a trilinear model, this data structure can also be included in MCR-ALS under the form of a constraint that can be applied to all or to some compounds [54–56,101].

As mentioned at the beginning of this section, an immediate consequence of analysing several chromatographic runs together is the improvement in the quality of the resolved profiles (elution profiles and spectra). Particularly, the most flexible methods that do not have limitations in handling differences in the elution pattern among runs open a wide field of possibilities. For instance, mixtures of main compounds and impurities can be eluted under different conditions (e.g., pH or mobile phase composition) to change the elution pattern of the sample and help in a better detection and quantification of the unknown impurities [13]. Alternatively, total analysis time for routine determinations can be considerably shortened with fast chromatography methods if the decrease in chromatographic resolution is compensated by appending a 'reference run' obtained with a longer analysis time and better chromatographic resolution [68,102]. In the same manner, analytes in complex samples, such as environmental samples, can be much better resolved from the interferences in the sample run if chromatograms with pure analyte standards are appended [69,103–105].

Although the improvement in the qualitative chromatographic information is a relevant issue, the possibility to obtain quantitative information is the most exploited and valuable aspect of the simultaneous analysis of several chromatographic runs. The main reason is the so-called second-order advantage, which allows for the quantification of the analytes in the presence of unknown interferences [55,56,106,107]. Let us imagine a data set formed by chromatograms of analyte standards with different concentrations and the chromatogram of a sample that contains the analyte in the presence of interferences (see Fig. 6). When we proceed to resolve the data set, we manage to separate the information linked to the analyte from the information due to the interferences, i.e., we obtain the pure elution profiles and spectrum for the analyte and for each interfering compound. Then, taking only the resolved elution profiles of the analyte in the different runs and estimating a quantitative parameter (peak area, A, or peak height, h), we may construct a classical calibration line with the pure standards and derive the concentration of the analyte in the unknown sample (see Fig. 6) [68,88,99,102–106]. As an additional outcome, we also obtain information about the interferences because their elution profiles and pure spectra are obtained. The most important part of the quantification procedure is that we may work with pure standards and we do not need to know the identity of the interfering species nor introduce them in the calibration samples. This is a crucial difference between these methods, which work with chromatographic data

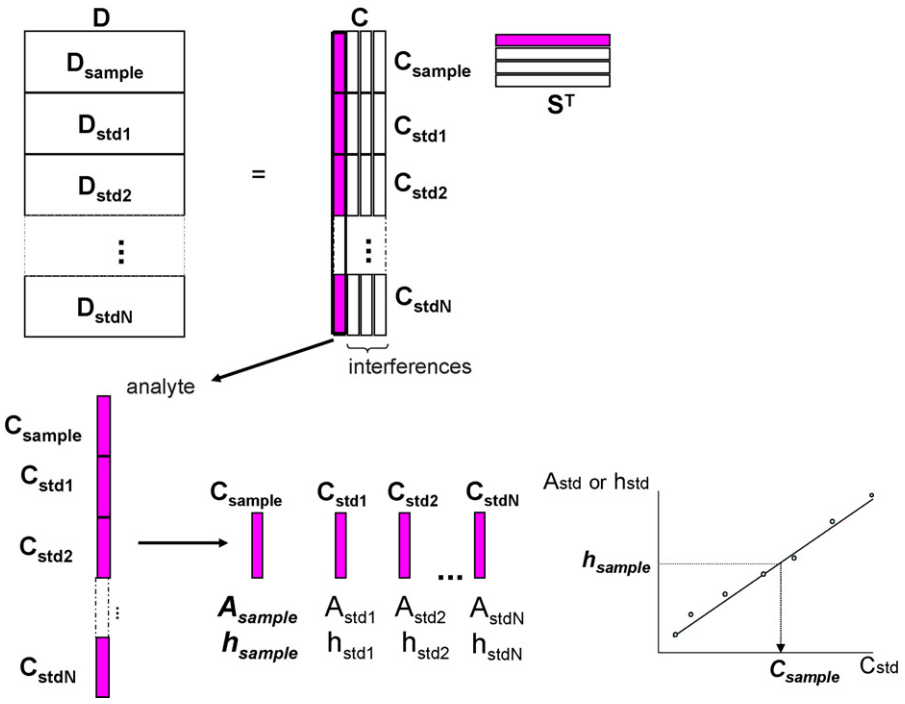

Fig. 6. Data arrangement and resolution of a sample run and standards to obtain quantitative information.

tables and resolve each particular compound, and classical multivariate calibration methods, which work with chromatographic vectors (e.g., a chromatogram registered at a single wavelength) and need to include all the interferences in the calibration samples. It should also be stressed that being able to work without introducing the interferences in the calibration samples saves a lot of time in terms of interference identification and implies a large reduction in the number of calibration samples. Actually, in the most extreme of the cases, a single calibration sample is enough to perform analyte quantification, as always happens in the GRAM method.

There are additional advantages linked to the way quantitative information is obtained with resolution methods. From Fig. 6, it can be clearly seen that the resolution process provides, by chemometric means, selective information about our analytes, i.e., the pure elution profiles are obtained. Hence, a classical calibration line can be derived, where a univariate measurement (peak height or peak area) is represented vs. the analyte concentration. As a consequence, figures of merit very well defined in univariate calibration can be applied in a straightforward manner to estimate the quality of the quantitative results coming from these complex data sets [107–109]. Since the final step of the quantification process is analogous to univariate calibration approaches, it is worth mentioning that strategies often adopted to solve chemical problems linked to the univariate quantification in chromatography can be translated to the multivariate chromatographic monitoring. Thus, the standard addition method can be used to cope with chemical matrix effects that can result in different analyte signal sensitivities between pure aqueous standards and the analyte in the sample. In this case, the different runs analysed would come from the sample spiked at different concentration levels (still, in this case, pure aqueous standards could be included in the analysis to improve the qualitative shape of the profiles recovered, although they would be discarded for quantification purposes) [87,110]. In the same way, internal standards could be used in each run when there is a poor reproducibility in the chromatographic signal. In both standard addition and internal standard strategies, the parameters represented in the calibration lines would be identical to those used in the equivalent univariate approaches. Other problems, such as the non-linearity of mass spectrometry responses, which could affect quantification, are also solved using classical strategies, such as developing local calibration models that cover small concentration ranges where the response can be considered linear. If the preference is using a global model, the quantitative information coming from the multivariate resolution method, i.e., the resolved peak area or the resolved peak height, can be fitted to a non-linear calibration model that relates signal measured and concentration.

Quantification in chromatography is often linked to analytical determinations of a particular compound in a series of independent samples. However, the qualitative and quantitative information gathered from the chromatographic resolution can go beyond this point if the samples analysed together maintain certain relationship among them, such as several aliquots collected during a process. Process monitoring by chromatography offers advantages over traditional spectroscopic monitoring, where a spectrum is collected in the solution sample (with all process components together) as a function of the process variable (time, pH, . . .). In chromatography, we obtain a data table at each stage of the process and the process components show differences both in the spectral shape and in the elution pattern. When we resolve these data sets, the identity of the components (pure spectra) is much better established because they can

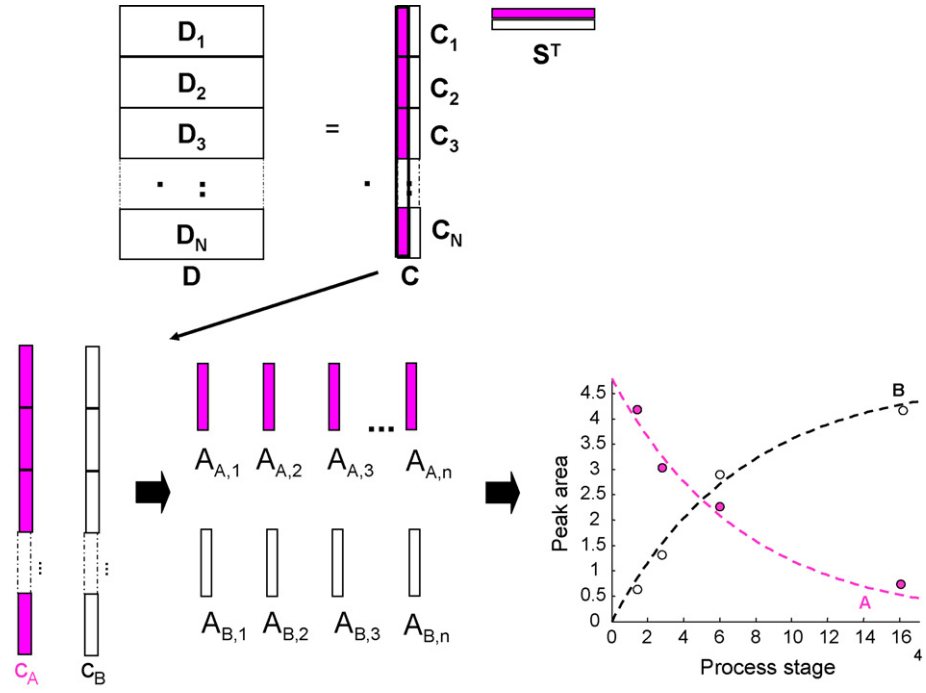

Fig. 7. Data arrangement, resolution and derivation of process profiles for a data set from a process monitored chromatographically.

show identical process profiles but they elute separately. The quantitative information, i.e., how the peak area of each particular compound changes from run to run, yields the process profile of the compound (see Fig. 7). The overall process model is obtained when the quantitative information of all the eluted process compounds is plotted vs. the value of the process variable at which the different aliquots have been taken from the bulk process solution. This strategy has been applied to study degradation processes of pesticides and has been proven to be particularly efficient in processes with complex pathways, where many components can evolve in identical way [111–114]. From the process profiles obtained, kinetic or thermodynamic models can be fit that confirm the mechanism suggested by the chromatographic results and provide physicochemical parameters of interest [114].

The flexibility of data arrangements that can be analysed by the methods of this section has allowed tackling challenging situations, such as the analysis of chromatographic runs with multiresponse detection. Several LC–DAD-MS runs have been resolved using MCR-ALS appending matrices not only in the elution direction but also in the response direction [115]; in this case, the combination of both responses in a single analysis reinforces the quality of the results obtained. It is also interesting going back to the compound observability concept to realize that the multiresponse detection can help to distinguish components that can share an identical spectrum in a particular technique (e.g., isomers with identical UV spectra) and be different according to another response detector, such as MS.

Regular data cube arrangements and their related methods (PARAFAC, GRAM, ...) have been proven to be useful in dealing with two-dimensional chromatographic data with a multivariate response, sized (retention time$_1$ × retention time$_2$ × response) [116,117] or to deal with several two-dimensional chromatographic runs conveniently aligned [118]. Using the regular cube arrangements, four-way data formed by several (GC × GC × MS) runs could be analysed in a metabolomic problem. In this case, four profiles were obtained per compound, namely the two elution profiles of the two chromatographic dimensions, the pure response and the quantitative information on the relative concentration of the compound in the different samples [119].

From the last examples, an important conclusion can be drawn. The diversity of techniques prepared to deal with several chromatographic data sets at the same time should necessarily solve many chemical problems that have appeared or may be new in the future. Thus, techniques prepared to deal with extended data arrangements, such as those in Fig. 5c, should allow for the simultaneous analysis of any kind of multirun and/or multiresponse combination, with complete freedom of shape in the elution direction and no limit to the diversity of responses collected. On the other hand, techniques that need regular cube data arrangements, such as those in Fig. 5a, are prepared for chromatographic runs which intrinsically have synchronisation in all data directions, such as multidimensional chromatography data, and may allow extending the analysis to chromatographic data with four informative directions or beyond.

6. Conclusions

It has been shown how the use of factor analysis methods can help to gather information from chromatographic data sets. These methods are of great help to handle the increasingly common outputs from hyphenated chromatographic techniques that provide chromatographic data tables in each analysis. Analysis

of single or simultaneous chromatographic runs with these powerful tools increases the knowledge about the nature of samples, with the characterization of known and unknown elution components, reduces the analysis time and allows for quantification in the presence of unknown interferences. The flexibility of data arrangements allowed by these tools and the power to handle very complex data sets in terms of size, number of overlapping compounds and diversity of responses and chromatographic schemes, ensures that the application of FA methods will be able to cover the needs of the most challenging chromatographic problems now and in the near future.

Although this review has been mainly focused on the description of the recent research done to develop and apply data analysis tools for chromatography, a last point of consideration could be wondering why these powerful tools are still generally underused in the daily work and how this can be solved. A shared effort between the tool developers, the instrument manufacturers and the end users could be the answer. Thus, research should be done to automate as much as possible the application of this methodology and to provide user-friendly software that does not require much decision making. In this sense, increasing the robustness of the methods and providing clear figures of merit and diagnostic tools to assess the quality of the results obtained is an essential point. The introduction of these methods in the instrumentation software is also crucial to spread their knowledge and application by end users. And, finally, the feedback of the daily users, expert in the nature of the chromatographic measurements, closes the loop and is essential to detect the real needs and problems unsolved by the current data analysis tools and to bring the research forward towards better and more efficient methods to handle chromatographic data.

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