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Trilinear chemometric analysis of two-dimensional comprehensive gas chromatography–time-of-flight mass spectrometry data

Amanda E. Sinha [a], Carlos G. Fraga [b], Bryan J. Prazen [a], Robert E. Synovec [a,*]

[a] *Department of Chemistry, Center for Process Analytical Chemistry, Box 351700, University of Washington, Seattle, WA 98195-1700, USA*
[b] *Department of Chemistry, 2355 Fairchild Dr. Suite 2N225, United States Air Force Academy, Colorado Springs, CO 80840-6230, USA*

Abstract

Two-dimensional comprehensive gas chromatography (GC × GC) is a powerful instrumental tool in its own right that can be used to analyze complex mixtures, generating selective data that is applicable to multivariate quantitative analysis and pattern recognition. It has been recently demonstrated that by coupling GC × GC to time-of-flight mass spectrometry (TOFMS), a highly selective technique is produced. One separation on a GC × GC/TOFMS provides retention times on two chromatographic columns and a complete mass spectrum for each component within the mixture. In this manuscript, we demonstrate how the selectivity of GC × GC/TOFMS combined with trilinear chemometric techniques such as trilinear decomposition (TLD) and parallel factor analysis (PARAFAC) results in a powerful analytical methodology. Using TLD and PARAFAC, partially resolved components in complex mixtures can be deconvoluted and identified using only one data set without requiring either signal shape assumptions or fully selective mass signals. Specifically, a region of overlapped peaks in a complex environmental sample was mathematically resolved with TLD and PARAFAC to demonstrate the utility of these techniques as applied to GC × GC/TOFMS data of a complex mixture. For this data, it was determined that PARAFAC initiated by TLD performed a better deconvolution than TLD alone. After deconvolution, mass spectral profiles were then matched to library spectra for identification. A standard addition analysis was performed on one of the deconvoluted analytes to demonstrate the utility of TLD-initiated PARAFAC for quantification without the need for accurate retention time alignment between sample and standard data sets.

Keywords: Chemometrics; Gas chromatography, comprehensive two-dimensional; Deconvolution; Parallel factor analysis

1. Introduction

Recently, the combination of two-dimensional comprehensive gas chromatography (GC × GC) with time-of-flight mass spectrometry (TOFMS) has become an active area of research [1–6]. Not only is GC × GC/TOFMS an excellent instrument for the identification of components in complex mixtures, but it is capable of generating trilinear data, thus broadening the opportunity to utilize state-of-the-art chemometric signal deconvolution techniques. It is essential to utilize this resulting trilinear data structure in order to realize the full power of the GC × GC/TOFMS technology and to optimize the extraction of useful information from each complex sample or from complex regions of otherwise simpler samples.

A trilinear data structure is a relatively high level structure [7]. Like non-negative data structure, unimodal data structure and linear data structure, trilinear data structure can be a useful tool for the interpretation of chromatographic data. The trilinear data structure as provided by the GC × GC/TOFMS instrument is described in Section 2. Qualitative and quantitative chemometric techniques continue to become more important tools for analytical chemists as analytical techniques are hyphenated and instruments continue to collect data faster than their predecessors. GC × GC/TOFMS is a perfect example of a state-of-the-art hyphenated instrument that creates a seemingly unmanageable amount of data, yet has the potential to more fully describe the contents of complex chemical mixtures.

Current peak deconvolution methods typically used for GC × GC/TOFMS data analysis are those that are already used for GC–MS. These methods require a purely selective mass channel and peak width/shape estimates. Furthermore, the current GC–MS peak deconvolution methods that are applied to GC × GC/TOFMS data resort to reducing the

* Corresponding author. Tel.: +1-206-685-2328; fax: +1-206-685-8665.
E-mail address: synovec@chem.washington.edu (R.E. Synovec).

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data into a series of two dimension GC–MS data, doing the analysis of each "second separation dimension slice" independently, and then recombining these results along the first separation dimension for the final assessment. However, with the added third dimension of selectivity and separation as in GC × GC/TOFMS, only partial selectivity is needed in both separation dimensions and the mass spectral dimension for peak deconvolution using a single data set, and the information along all three dimensions is analyzed simultaneously. Herein, we report that the trilinear data structure naturally provided by GC × GC/TOFMS combined with the appropriate chemometric techniques allows for deconvoluted chromatographic profiles and mass spectra to be produced without specifying selective mass signals and without resorting to requiring peak shape and width estimates. This work gives promise to future studies that will investigate the power of combining GC × GC/TOFMS with pattern recognition and multivariate quantitative classification methods that take advantage of the trilinear structure of the GC × GC/TOFMS data [8,9].

Chemometric calibration techniques such as the generalized rank annihilation method (GRAM), trilinear decomposition (TLD) and parallel factor analysis (PARAFAC) were developed to find relationships in trilinear data [7]. One method of generating trilinear data is to acquire a set of bilinear data, e.g. a set of multiple GC × GC analyses of a compound of interest at more than two concentrations. GRAM is used for analyzing two bilinear data samples at a time, while TLD was developed as an extension of GRAM, with TLD being capable of analyzing multiple bilinear data samples at once [7,10–14]. All of these calibration methods require that the data structure be trilinear, which implies that "the response in [all] domains of the instrument arising from a species should be unique, consistent, and independent of the presence of other species" [15]. When both chromatographic columns in GC × GC are subjected to temperature programming, the bilinear data integrity can come into question and must be substantiated [16].

With analytical instruments like GC × GC with flame ionization detection, calibration methods such as GRAM are able to deconvolute unknowns using two data sets (standard and sample) where the analytes of interest vary in concentration between the two data sets [12,17–22]. Using trilinear data, such as GC × GC/TOFMS data, it is possible to deconvolute individual components from a group of partially overlapped components using a data set from only one sample. This ability to deconvolute a single data set with partially resolved signals into the fully resolved signals is known as the third-order advantage [23]. In the case of chromatographic data, third-order data is also advantageous because it relaxes the requirements for sample-to-sample retention time precision thus essentially eliminating the need for retention time alignment prior to analyte deconvolution, identification, and quantification involving standard addition analysis.

In order to facilitate development of trilinear chemometric methods, an environmental sample containing fuel components, pesticides and natural products was separated with GC × GC/TOFMS. With the goal of demonstrating the chemometric techniques, not complete sample characterization, one representative region of overlapping peaks in the real, complex sample was analyzed with TLD and PARAFAC. It will be demonstrated that TLD and PARAFAC are able to deconvolute from initially partially resolved data, the pure component profiles in both chromatographic dimensions and the pure mass spectrum of each component. In addition, a procedure to identify and quantify components of interest in a complex mixture via a standard addition method is outlined. This analysis procedure is successfully demonstrated for an analyte of interest in the environmental fuel sample without requiring retention time alignment between sample and standard addition cases.

2. Theory

2.1. Trilinear data

Mathematically, the trilinear parallel factor analysis model is described as:

$$\boldsymbol{R} = \sum_{n=1}^{N} \boldsymbol{x}_n \otimes \boldsymbol{y}_n \otimes \boldsymbol{z}_n + \boldsymbol{E} \tag{1}$$

where $\boldsymbol{R}(I \times J \times K)$ is the instrument response matrix, $\boldsymbol{x}_n$, $\boldsymbol{y}_n$, and $\boldsymbol{z}_n$ are the nth columns of the matrices $\boldsymbol{X}(I \times N)$, $\boldsymbol{Y}(J \times N)$, and $\boldsymbol{Z}(K \times N)$ containing the N pure component profiles in each dimension. $\boldsymbol{E}(I \times J \times K)$ is the error matrix, e.g. noise. For GC × GC/TOFMS data, the dimensions are the column 1 separation ($\boldsymbol{X}$), the column 2 separation ($\boldsymbol{Y}$), and the mass spectrum ($\boldsymbol{Z}$). The trilinear model as applied to GC × GC/TOFMS data is illustrated graphically in Fig. 1. Data with the trilinear structure, like GC × GC/TOFMS data, is advantageous because signals which are not completely resolved by the instrument can often be mathematically resolved if there is some selectivity in each of the three dimensions. This mathematical

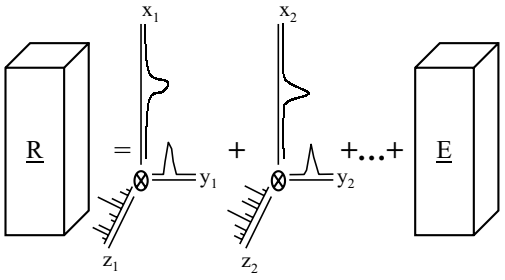

Fig. 1. Illustration representing the trilinear data structure of GC × GC/TOFMS data. For the instrument response $\boldsymbol{R}$ there are unique profiles in both chromatographic dimensions ($\boldsymbol{x}_n$ and $\boldsymbol{y}_n$) and a unique mass spectrum ($\boldsymbol{z}_n$) for each component in a data matrix with N components, which can be described mathematically as $\boldsymbol{R} = \sum_{n=1}^{N} \boldsymbol{x}_n \otimes \boldsymbol{y}_n \otimes \boldsymbol{z}_n + \boldsymbol{E}$ where $\boldsymbol{E}$ is error (e.g. noise).

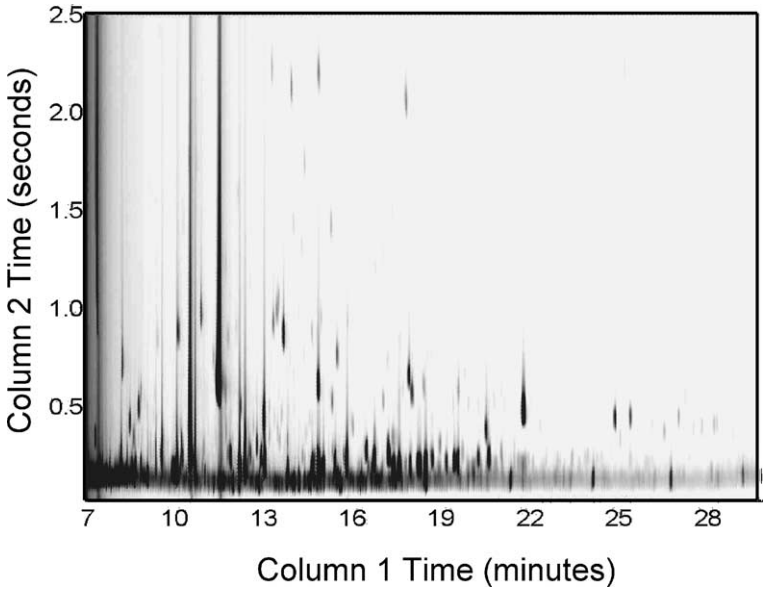

Fig. 2. Total ion current (TIC) chromatogram of a complex environmental sample.

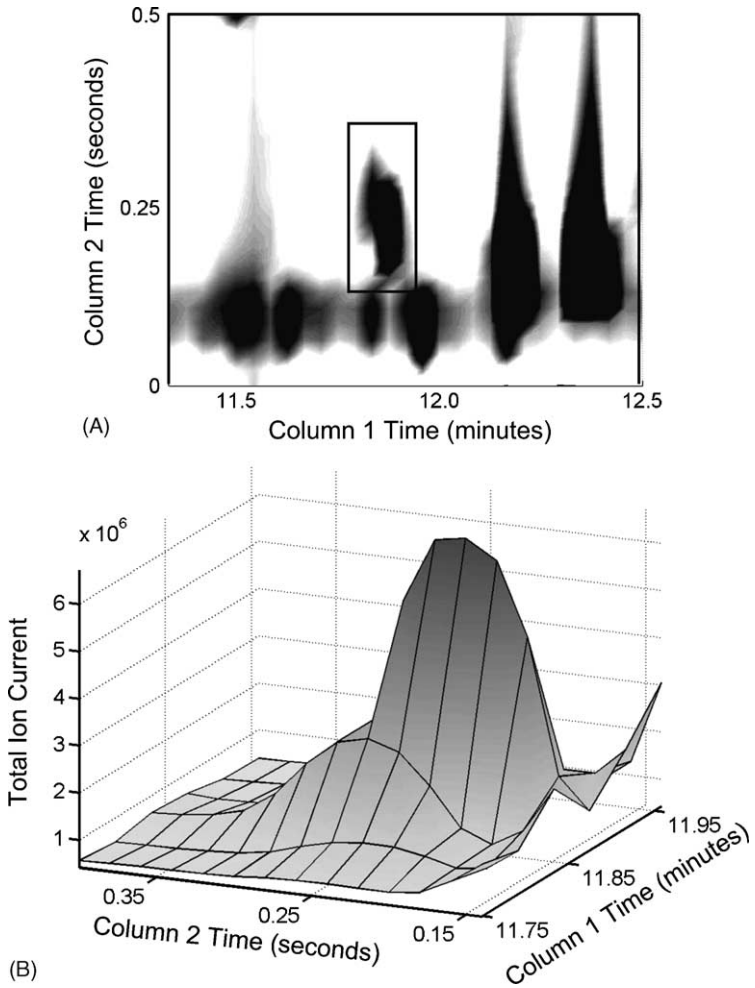

Fig. 3. (A) Region of the TIC of the environmental sample (Fig. 1) that contains overlapped peaks as indicated by overlaid box, (B) three-dimensional image of the sub-region in the box outlined in A.

resolution, or deconvolution, does not require peak shape assumptions or completely selective mass channels.

2.2. Trilinear decomposition (TLD) and parallel factor analysis (PARAFAC)

TLD and PARAFAC are chemometric techniques that have been well documented in the literature [7,10,24–26]. TLD is an eigenvalue-based solution to the trilinear PARAFAC model [10,27]. The alternating least squares (ALS) based solution to the trilinear PARAFAC model has acquired the name PARAFAC and is the most popular method. PARAFAC deconvolution uses a starter solution, in these experiments the TLD results, followed by ALS to find a solution to the model [25,26]. Other possible starter solutions include random values, random orthogonalized values and singular values. We found that TLD initialization was the fastest approach and gave the best results for GC × GC/TOFMS data. TLD is advantageous because it does not require a starter solution and because it is computationally fast. But for the data in this manuscript, TLD followed by PARAFAC deconvolution gives better results than TLD alone. Superior deconvolution with PARAFAC agrees with the findings of other authors [26]. The strength of PARAFAC deconvolution is mainly attributed to non-negative and unimodal constraints that are incorporated into the PARAFAC deconvolution algorithm.

3. Experimental

An Agilent 6890 gas chromatograph equipped with an Agilent 7683 auto-injector (Agilent Technologies, Palo Alto, CA, USA) was modified to a high-temperature valve-based GC × GC system by mounting the wetted portions of the high-speed six-port micro-diaphragm valve (VICI, Valco Instruments, Houston, TX, USA) inside the oven and the remaining portions outside the oven, freely exposed to room air [28]. The second column was then connected to a Leco Pegasus III TOFMS system (Leco, St. Joseph, MI, USA) via the heated transfer line. Additional details about the instrument have been recently reported [6,29]. A GC × GC/TOFMS analysis was performed on a complex environmental sample to demonstrate the separation and performance characteristics of the new configuration. A complicated region of the environmental sample was then analyzed using TLD and PARAFAC to investigate the peak deconvolution capabilities of these techniques combined with the GC × GC/TOFMS data.

The first column (column 1) of the GC × GC/ TOFMS for the complex environmental sample analysis was a 60 m × 250 μm i.d. capillary column with a 0.5 μm 5% diphenyl–95% dimethylpolysiloxane film (DB-5; J&W Scientific/Agilent Technologies). The second column (column 2) was a 3 m × 180 μm i.d. capillary column with a 0.05 μm 90% biscyanopropyl–10% phenylcyanopropyl film (RTX-2330; Restek, Bellefonte, PA, USA). Helium was used as the carrier gas. Column 1 was operated with a constant flow of 1.0 ml/min. Column 2 was operated with a constant pressure of 20 psi (1 psi = 6894.76 Pa). The injector set point was 275 °C and 2.0 μl injections of the environmental sample were splitless for 0.5 min. The oven was held at 40 °C for 0.5 min, ramped to 80 °C at 20 °C/min, ramped to 210 °C at 5 °C/min, then ramped to 230 °C at 20 °C/min and held for 4 min. The valve was equipped with a 5 μl sample loop and actuated every 2.5 s with a 60 ms injection pulse width. A novel stand-alone pulse generator that was designed and built in-house was used to control the valve actuation. This new hardware allows the user to set the pulse width, the period of the actuations, and the total duration of the analysis. This new development replaces the LabVIEW 6i (National Instruments, Austin, TX, USA) program and counter/timer board [6,29]. The mass spectrometer had a transfer line temperature of 250 °C and an ion source temperature of 200 °C. The filament bias voltage was −70 V and the detector voltage was −2000 V. All other

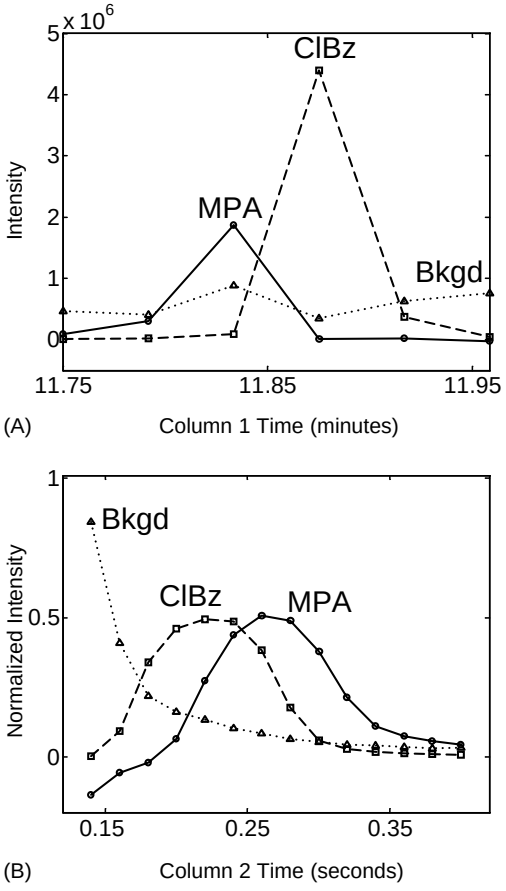

Fig. 4. Trilinear decomposition (TLD) peak profile results for deconvolution of two chemical components in the environmental sample. Three of the four components are shown: MPA, ClBz and background interferents (Bkgd). (A) Column 1 pure component profiles, (B) column 2 pure component profiles. MPA and ClBz are identified by the deconvoluted mass spectra in Fig. 5. The fourth component modeled was "baseline", omitted for clarity.

MS parameters were set from the results of an automatic optimization sequence controlled by the Leco software using perfluorotributylamine (PFTBA) as the standard. Data were collected from *m*/*z* 40 to 300 at a nominal rate of 5 kHz and averaged to 50 full spectra/s by the Leco software. Data were then exported as a comma separated value (.csv) file and loaded into Matlab 6.0 R12 (The Mathworks, Natick, MA, USA) for data processing. The algorithm for TLD was from the PLS_Toolbox (Eigenvector Research, Manson, WA, USA) and was chosen because of the advantageous ordering of the three dimensions of the matrix prior to analysis. The PARAFAC algorithm was from the N-way Toolbox 2.10 [30]. Chlorobenzene (ClBz) was used for a standard addition analysis such that the added amount was 4.3 μg/ml in the environmental sample (Alfa Products, Thiokol/Ventron Division, Danover, MA, USA).

4. Results and discussion

A total ion current (TIC) chromatogram of the complex environmental sample is shown in Fig. 2. Even though the overall separation achieved on the environmental sample was good, there were instances where components are not fully resolved with the two-dimensional chromatography. This is a common occurrence for highly complex samples. One such instance in the environmental sample is shown in Fig. 3A. The sub-region defined by the inset box in Fig. 3A is depicted in Fig. 3B as a three-dimensional image. In this region, there are two main components as well as some background (Bkgd) and baseline interferents. The feasibility of using TLD and PARAFAC with data from this instrument was investigated using these overlapped components as analytes and the

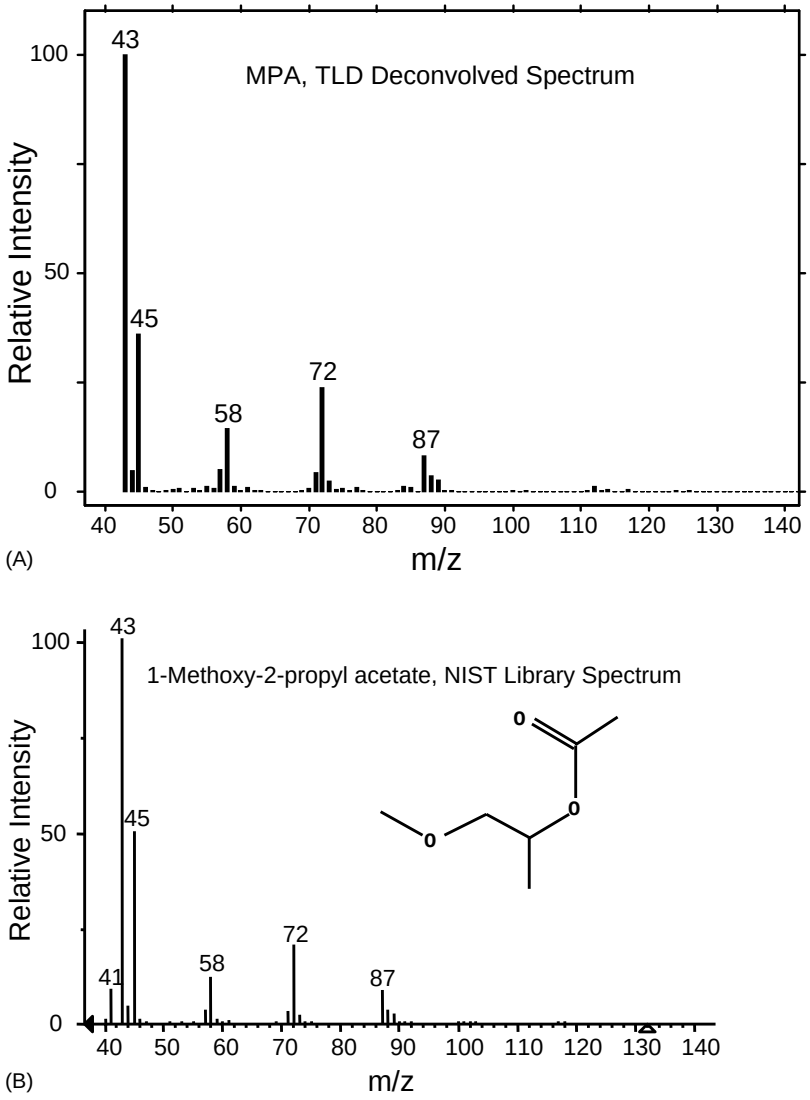

Fig. 5. Trilinear decomposition (TLD) mass spectral profile results for deconvolution of two components in the environmental sample. MPA is 1-methoxy-2-propyl acetate. ClBz is chlorobenzene. (A) Deconvoluted mass spectrum for analyte MPA, (B) NIST Library mass spectrum of MPA, (C) deconvoluted mass spectrum for analyte ClBz, (D) NIST Library mass spectrum of analyte ClBz. Further, confirmation of the identity of analyte ClBz as chlorobenzene was achieved through standard addition.

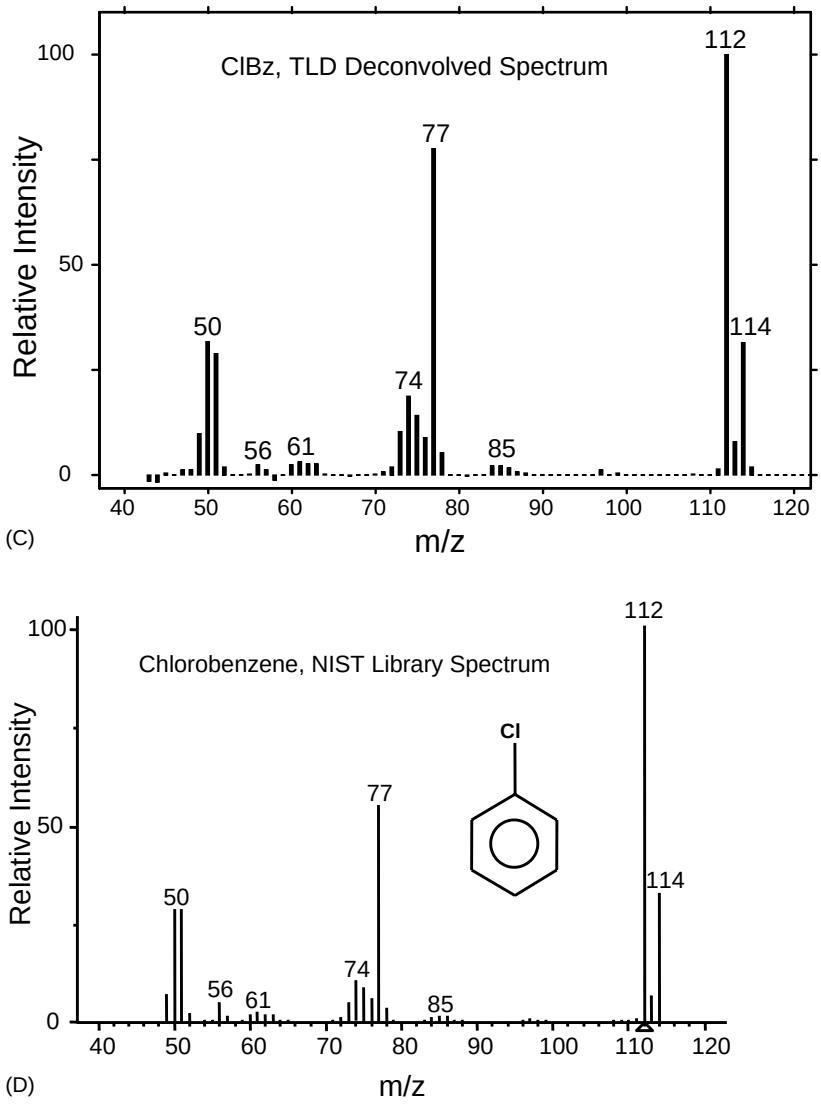

Fig. 5. (*Continued*).

region shown in Fig. 3, as the known elution region of the analytes.

Fig. 4A and B are the columns 1 and 2 peak profile results of TLD deconvolution, respectively. The TLD model was developed with four components (i.e. factors), but only three are shown for clarity, the fourth being mostly baseline offset which was not subtracted prior to deconvolution. Columns 1 and 2 pure component profiles are reasonably good, although there is some deviation from conventional chromatographic peak shape in the column 2 profile of component labeled 1-methoxy-2-propyl acetate (MPA). This is indicative that the TLD model is not able to completely deconvolute component MPA from the sloping edge of the adjacent background signal labeled "Bkgd" because of insufficient selectivity on column 1 (Fig. 4B). The background signal is comprised of additional, unknown interferences. TLD also provides the deconvoluted mass spectra. Based on the deconvoluted mass spectra results, the sample subregion was found to contain 1-methoxy-2-propyl acetate and chlorobenzene, as well as some unknown background interferents. There are multiple factors to evaluate the quality of a spectral match in the U.S. National Institute of Standards and Technology (NIST) MS search program. The match factor evaluates how closely the target spectrum and the database spectrum correlate. It is calculated based on the inner product of the two spectra, with lower *m*/*z* peaks having less weight than higher *m*/*z* peaks. Values are reported on a scale from 1 to 1000 where a perfect match is 1000. The reverse match factor ignores impurity peaks in the experimental spectrum, that is, peaks that are not present in the library spectrum. This is also reported on a scale of 1–1000. The probability of the unknown spectrum arising from the same compound that generated the library spectrum is listed on a scale from 1 to 100. The mass spectrum of component MPA was matched to a spectrum of 1-methoxy-2-propyl acetate in the NIST Library with a match factor of 904,

a reverse match factor of 939, and a probability of 92.2 (Fig. 5A and B). The mass spectrum of component ClBz was matched to a spectrum of chlorobenzene in the NIST Library with a match factor of 933, a reverse match factor of 937, and a probability of 98.4 (Fig. 5C and D). The identity of component ClBz was confirmed with a standard addition of chlorobenzene into the original sample. The reverse match factor is higher than the match factor for component MPA indicating that there are some *m*/*z* values in the deconvoluted spectrum that are not present in the library spectrum. This is most likely due to the component "Bkgd" contributing to the deconvoluted mass spectrum for MPA due to the low resolution on column 1. The spectral match is still quite high and the identification is accurate. The chromatographic profiles on column 2, however, are not ideal. Even though the trilinear chemometric methods do not rely upon peak shape information for the deconvolution, the analyst often desires to obtain deconvoluted peak shapes of superior quality. Thus, reasonable chromatographic peak shapes should be strived for.

PARAFAC was employed on this same data in an effort to improve upon the peak deconvolution results obtained by TLD. The model was initiated with the TLD results shown in Figs. 4 and 5. Non-negativity constraints were imposed on all dimensions. The column 1 and column 2 peak shapes are improved by PARAFAC over the TLD results, which should enable more accurate quantification (Fig. 6A and B). Likewise, the deconvoluted spectra for analytes MPA and ClBz are shown in Fig. 7A and B. The mass spectrum of component MPA was matched to a spectrum of 1-methoxy-2-propyl acetate (Fig. 5B) in the NIST Library with a match factor of 879, a reverse match factor of 905, and a probability of 88.7. The match factor for MPA with the PARAFAC is slightly less than that of TLD, but the difference is not statistically significant. By comparing both deconvoluted spectra of MPA (Figs. 5A and 7A) with the library spectrum of 1-methoxy-2-propyl acetate (Fig. 5B), it can be seen that the ratios of the higher masses of the TLD result correspond better with the library spectrum than those for the PARAFAC result. This could be the cause of the slight decrease in match quality since the higher *m*/*z* ratios have more weight in calculating the match factor. The mass spectrum of component ClBz was matched to a spectrum of chlorobenzene in the NIST Library (Fig. 5D) with a match factor of 944, a reverse match factor of 948, and a probability of 98.5, indicating a very good identity match.

The above example indicates the GC × GC/TOFMS data is compatible with chemometric calibration techniques like PARAFAC and TLD that call for trilinear data structure. Even though some of the ions appear selective for each analyte, e.g. *m*/*z* 112 for chlorobenzene and *m*/*z* 43 for 1-methoxy-2-propyl acetate, the TLD and PARAFAC algorithms do not require selective ions. TLD and PARAFAC are able to deconvolute pure analyte profiles from complex mixtures as long as there is at least partial selectivity in each of the three dimensions. In general, very complex

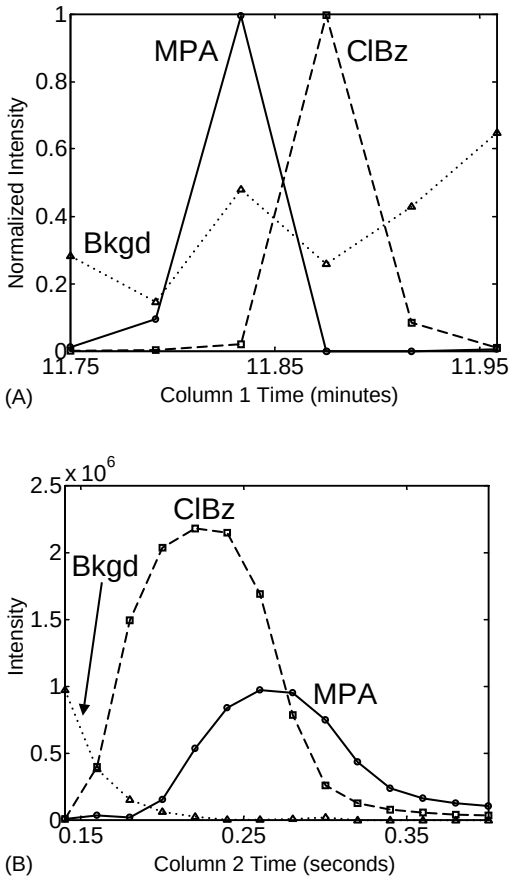

Fig. 6. PARAFAC peak profile deconvolution results for the overlapped region in the environmental sample using TLD results for initiation and using non-negativity constraints in all dimensions. As in Fig. 4, three of the four components are shown for clarity. (A) Column 1 pure component profiles, (B) column 2 pure component profiles.

samples may contain overlapped constituents that do not have a selective ion, e.g. isomers. We are currently studying complex samples with isomers in order to investigate more thoroughly this issue. Furthermore, unlike deconvolution methods developed for GC × GC with flame ionization detection, TOFMS detection provides additional structure to the data, which allows for deconvolution using trilinear-based methods without the comparison of data sets. This substantially relaxes retention time reproducibility requirements and makes for a more reliable deconvolution. The selectivity of TOFMS substantially reduces the probability of unresolved signals as well.

From this initial study, a four-step procedure has been developed to deconvolute, identify and quantify analytes of interest that are not fully resolved nor have a fully selective mass channel. First, two data files are collected: a "sample" and a "sample + standard addition," in which quantitative amounts of all the analytes of interest are spiked into the standard addition. TLD followed by PARAFAC is performed on the region around each analyte of interest, which will give individual peak profiles and mass spectra for both data sets. The analytes in the sample data set are identified by

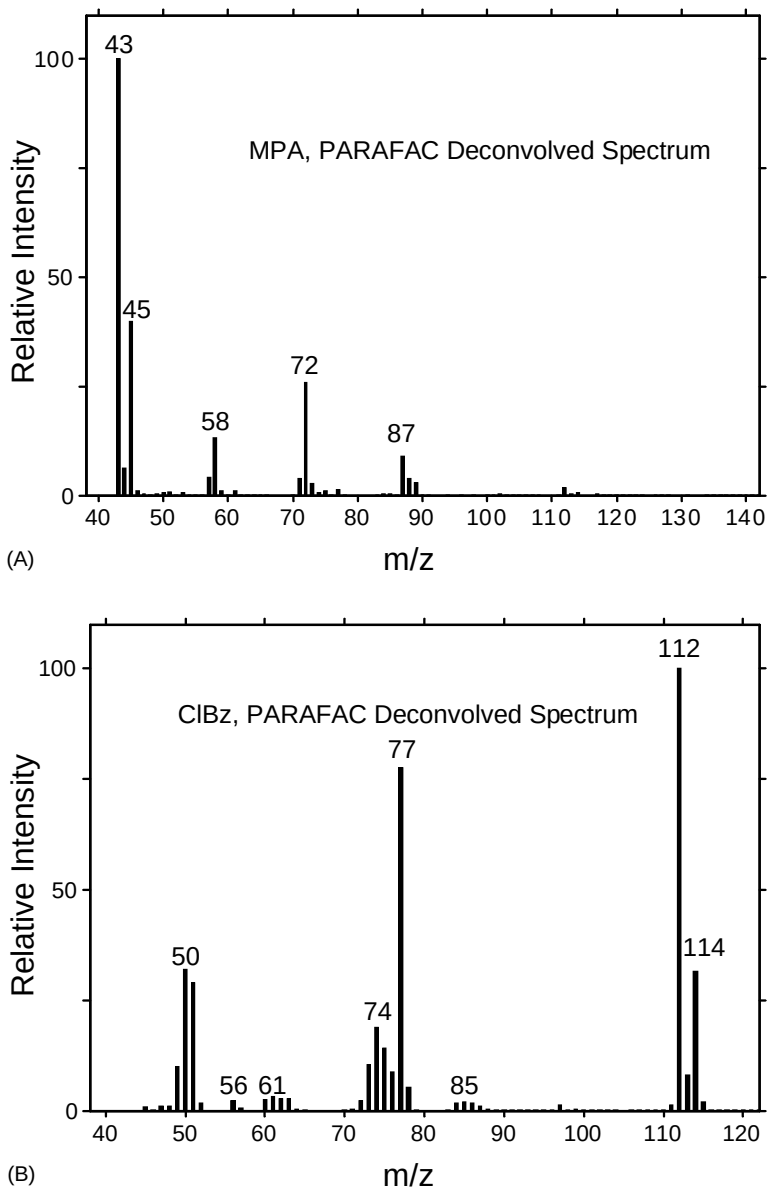

Fig. 7. PARAFAC mass spectral profile deconvolution results for overlapped region in the environmental sample using TLD results for initiation and using non-negativity constraints in all dimensions. MPA is 1-methoxy-2-propyl acetate. ClBz is chlorobenzene. (A) Deconvoluted mass spectrum for analyte ClBz. NIST MS search resulted in the same chemical identity as obtained for TLD results (Fig. 5B), (B) deconvoluted mass spectrum for analyte ClBz. NIST search resulted in the same chemical identity as obtained for TLD results (Fig. 5D).

comparing their deconvoluted mass spectra to those of the standard addition sample or to a MS library. Comparison to the standard addition sample can improve the quality of matches because the reference spectrum (i.e. standard addition sample) is obtained on the same instrument as the sample spectrum as opposed to the NIST Library spectra that are obtained on a number of different instruments resulting in different fragmentation ion ratios. Quantification is then achieved by reconstructing the signal of the analytes of interest in both data sets then applying signal integration and the usual mathematical techniques for quantification via standard addition. The fact that the deconvolution is performed separately on both the sample and the standard addition loosens the retention time alignment requirements, thus simplifying and improving the quantification process significantly. This analysis procedure was followed for the identification and quantification of chlorobenzene in the environmental sample. A chlorobenzene standard was spiked into the sample as a standard addition at the level of 4.3 μg/ml. Deconvolution was performed on a region of the standard addition data set containing the spiked standard. Reconstruction of the chlorobenzene peak and summing all of the mass channels to generate a TIC chromatogram was achieved for both the “sample” and “sample + standard addition sample.” The volumes for the sample and standard addition peaks calculated from the

respective TIC chromatograms indicated that the original concentration of chlorobenzene in the environmental sample was 1.4 μg/ml. Thus, quantification via standard addition without retention time alignment was successful using TLD-initiated PARAFAC. The precision and accuracy for TLD and PARAFAC are consistent with second-order methods such as GRAM and indicate TLD-initiated PARAFAC appears to perform better at lower chromatographic resolution than does GRAM. These attributes of TLD-initiated PARAFAC will be studied in more detail in future work.

5. Conclusions

It was demonstrated that the GC × GC/TOFMS trilinear data structure is compatible with chemometric calibration techniques such as TLD and PARAFAC. Successful deconvolution using PARAFAC initiated by TLD, followed by analyte identification was achieved on overlapped constituents in a complex environmental sample, requiring only a single data set for qualitative analysis. Analytes of interest in a mixture can be identified and quantified using a standard addition method combined with TLD-initiated PARAFAC, which would eliminate the need for peak shape predictions and retention time alignment between the sample and the standard prior to deconvolution. TLD-initiated PARAFAC also eliminates the need for fully selective mass channel ions for deconvolution; however, some selectivity is required in each dimension for the algorithm to be successful. Future work will be aimed to probe the limits of algorithm applicability with regard to quantitation, precision, and accuracy of the results. In addition, future work to automate this process for regions of interest will be addressed.

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