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Abstract: Blind Source Separation (BSS) techniques aim to extract a set of source signals from a measured mixture in an unsupervised manner. In the chemical instrumentation domain source signals typically refer to time-varying analyte concentrations, while the measured mixture is the set of observed spectra. Several techniques exist to perform BSS on Ion Mobility Spectrometry, being Simple-to-use interactive self-modeling mixture analysis (SIMPLISMA) and Multivariate Curve Resolution (MCR) the most commonly used. The addition of a multi-capillary gas chromatography column using the ion mobility spectrometer as detector has been proposed in the past to increase chemical resolution. Short chromatography times lead to high levels of co-elution, and ion mobility spectra are key to resolve them. For the first time, BSS techniques are used to deconvolve samples of the gas chromatography - ion mobility spectrometry tandem. We propose a method to extract spectra and concentration profiles based on the application of MCR in a sliding window. Our results provide clear concentration profiles and pure spectra, resolving peaks that were not detected by the conventional use of MCR. The proposed technique could also be applied to other hyphenated instruments with similar strong co-elutions.

Prof. Udo Weimar
Editor
Sensors & Actuators: B. Chemical

January 7th 2015

Dear Dr. Weimar,

Ms. Ref. No.: SNB-D-14-01966

Please find attached a revised version of our manuscript "Sliding Window Multi-Curve Resolution: Application to Gas Chromatography - Ion Mobility Spectrometry", which we would like to resubmit for publication in the IMCS 2014 Special Issue in Sensors & Actuators: B. Chemical.

The comments of the reviewers were very insightful and have enabled us to improve the quality of our manuscript. The following pages provide point-by-point responses to each of the comments of the reviewers. We hope that the revisions in the manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in Sensors & Actuators: B. Chemical.

We look forward to hearing from you at your convenience,

Yours sincerely,

Sergio Oller, in behalf of all the authors

Responses to the comments of Reviewer #2: (figure numbers updated to current paper status)
Reviewer #2: The paper deals with a very important point of data interpretation of MCC/IMS-Chromatograms.

The procedure starts with the estimation of the number of components within the mixture. The progress compared to the state of the art is visible for experts only, but not for the reader without detailed background in IMS data analysis. Some critical details are still missed:

- how the peak extraction works with low intensities?
The peak extraction performance is illustrated on figures 4-6.
- A region of interest is described at Fig. 4.
- The standard MCR-ALS technique is applied to that region, and the lower intensity peaks are not properly extracted (Fig. 5)
- The proposed SW-MCR technique is applied, extracting all the three peaks in the region.
Minor changes have been made to the Fig. 6 results and discussion to emphasize this.

Additionally, we have also added Table 1, that provides more insights on how MCR-ALS and SW-MCR perform on a larger set of peaks.

- what is X in Figure 1?
The last spectrum shown in window N+1 of Figure 1 is not linked to any of the spectra of the neighbour windows. Therefore, this spectrum is rejected from the final set of compounds. The "X" was meant to be

interpreted as a cross, marking the absence of a link. We have replaced the typographical “X” with a cross to reduce the chance of confusions.

- under point 2.3 a region from 4 to 14.65 ms is mentioned, but nothing was shown in figure 2 until 5.5 ms, why?

Fig 2 only shows the region from 5.5 to 12 ms because was not any significant peak outside this region in this sample. In the data analysis we chose a more conservative approach and kept a wider margin. Having a region without peaks in the analysis does not do any harm (except a slightly higher computational cost), but cutting the head or tail of a peak on the other hand could be very harmful.

- the window length was selected on typical width if a peak within the chromatogram - should be specified further in detail

We have given further specifications:

The window length was selected based on the typical width of a peak in the chromatogram, computed as the median full width at half maximum of ten representative peaks in the sample.

- what is the effect of lager window sizes and smaller window overlaps?

We have added this paragraph on section 2.4:

Larger window sizes and smaller window overlaps may be used to reduce the computational cost of the method. A larger window size would imply that more compounds can be found in the same window, if the window is too large we will face the same problem than with conventional MCR-ALS application and we may fail to detect local peaks with low intensities. Regarding the window overlap, a too small window overlap would increase our chances of splitting peaks in window borders and would hinder our ability to distinguish spurious solutions from actual compounds, as actual compounds would not have to consistently appear among consecutive windows anymore.

- in case typical RIP - see figure 3 is in the range of 80.000 units, why typical peaks in the range of 2000 are considered in figure X [old figure 4 was removed as suggested] - the range og minimum of RIP as shown in figure 2 s about 10.000 - are there different a.u.?

Yes, the reverse RIP shown in Figure 3, is based on the integration (sum) of the full RIP peak, ranging from 6.25 to 6.6 ms. Figure X(removed) shows a single spectrum and therefore its arbitrary units are much smaller.

We have clarified both the caption and the y axis of the figure to remove any further confusion.

- figure 4 could be delected - the effect of base line correction will be known!

Thank you for the suggestion. We have removed it.

- figure 5 - in case the RIP is at 80.000 - how the peak could be at 120.000?

Figure 5 shows the concentration profiles and pure spectra of the resolved MCR-ALS peaks. Each peak in the sample is deconvolved on a normalized pure spectra (shown on the left) and its concentration profile (on the right). Therefore, arbitrary units of the sample are obtained by convoluting the concentration profile with the pure spectrum. As an example for this particular case, the normalized pure spectra has a maximum peak intensity of 0.023 at drift time = 10ms and its concentration profile peaks at 45s with 1.05E5. Convoluting both spectra will give a maximum at retention time 45s, drift time 10ms, with intensity 0.023x1.05E5 = 2415. This intensity value is measured in the arbitrary units of the sample and matches the intensity value obtained on that specific time region at figure 4.

- figure 7 - what is the message?

Figure 7 confirms that SW-MCR is able to deconvolute multiple co-eluting compounds, and that the deconvolution is consistent with the co-elution levels found in Figure 2 and Figure 3. We have clarified the paragraph in the text.

- figure 9 suggests, that in each retention time window - same width - 1 or 2 peaks were found in minimum

Yes. In fact, as figure 7 shows, the Reactant Ion Peak is detected in all the windows. Given the degree of co-elution shown on the first 70 seconds of Fig. 2, it is not surprising that other compounds are also detected on almost all the windows.

- figure 9 - the broadening of peaks with retention time was not considered

No, the broadening of peaks was not considered. We considered a fixed window length for all the windows, and that window length determines the width of the bins on Fig. 9. Using a variable window length depending on the broadening of the peaks might improve the performance of the method, but it would also increase its complexity (as more parameters would be needed to describe how the window length changes).

- figure 4: why a lower number of components compared to the 3D plot from figure 2 was considered - would be nice to see an analysis on IMS-Chromatogram shown in figure 2 for direct comparison - should be shown, please

The region shown on figure 4 was considered instead of the whole region from figure 2 in order to provide a simple and clear example of a region with both high and low intensity peaks that co-elute. In order to provide more details on the comparison between methods, Table 1 has been added showing a list of 22 peaks from the sample and their detection in both methods. The corresponding paragraph on the results section has been changed as follows:

The performance of the proposed SW-MCR method has been assessed by comparing the extracted concentration profiles and pure spectra with the ones resolved using conventional MCR-ALS on the whole sample, using the same described pre-processing and imposing the same constraints. Regions with strong co-elution are of particular interest, as for those regions conventional MCR-ALS is not able to resolve all compounds, especially the smallest ones. 22 peaks of the first 100 seconds of the sample were selected randomly (covering higher and lower peak intensities) and we checked the retention time range where each peak had been detected by each method. Table 1 shows the actual retention time range of the sample and the one obtained by each method. When the peaks are detected, there is good agreement between both methods; however MCR-ALS failed to detect 9/22 of the analyzed peaks.

- figure 4 shows large tailing of a peak at 10 ms, means peaks of components with lower proton affinity are not detectable - it´s an rather overloading situation - what happens at 7.6 ms?

As the 10ms peak fades, a 7.6 ms a peak appears starting from retention time 40 seconds. This peak lasts a long time in the sample. This may be caused by some memory effect of the spectrometer.

Summarizing, the papers shows an important method, but the story should be improved further before publishing.

Responses to the comments of Reviewer #3: (figure numbers updated to current paper status)

Reviewer #3: The authors present an alternative approach to MCR-ALS for blind source separation problem for gas chromatography - ion mobility spectrometry. The method uses a sliding window tracking the local peaks selected by using singular value decomposition. Each of the compounds are tracked following the temporal structure based on the similarities of the profiles. The idea is simple and appears to work nicely. The simpler the better. In my opinion this a better suited method than MCR-ALS. First, because it is linear and, second, because it does not warranty convergence. So I think the authors propose a significant improvement. Fig 9 is a confirmation that the proposed method can pretty much track most of the SVD components, which is nice to verify.

The authors apply their method to olive oil classification and show how the sliding-tracking window method can detect more traces than MCR-ALS.

A major concern is that I'd like to have a confirmation of these results by using GC-MS. This would be the ultimate test to know that their proposed solution is the appropriate one.

This is indeed an interesting suggestion and it would provide a nice comparative, however we feel it falls outside the scope of this study.

Some minor comments

Please succinctly explain what co-elution is in the Introduction.
We have added this sentence in section 1:
However, as MCC's are characterized by presenting short chromatography times, multiple compounds may still elute from the column at the same time (co-elute).

Provide references for "However, in MCC-IMS chromatography conditions, co-elution is the rule instead of the exception". Consider changing the sentence to something like "co-elution is a prevalent phenomena"
Thank you for the suggestion. Some references have also been added.

Abstract replace "on an unsupervised manner" by "in an unsupervised manner".
Thank you. Corrected.

Abstract: Replace "Results provide clear concentration profiles" by "Our results provide clear concentration profiles"
Thank you. Corrected.

The norms of equation 2 and 3 are missing.
Fixed. Missing font issue. Thank you.

In Fig. 2 it is confusing to have the x and z axis running in opposite directions to what one would expect from the natural order of numbers.
We agree it may be confusing and we have clarified the figure legend accordingly. We chose that axis direction to avoid larger peaks hiding the smaller ones.

Sliding Window Multi-Curve Resolution: Application to Gas Chromatography - Ion Mobility Spectrometry

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Abstract

Blind Source Separation (BSS) techniques aim to extract a set of source signals from a measured mixture in an unsupervised manner. In the chemical instrumentation domain source signals typically refer to time-varying analyte concentrations, while the measured mixture is the set of observed spectra. Several techniques exist to perform BSS on Ion Mobility Spectrometry, being Simple-to-use interactive self-modeling mixture analysis (SIMPLISMA) and Multivariate Curve Resolution (MCR) the most commonly used. The addition of a multi-capillary gas chromatography column using the ion mobility spectrometer as detector has been proposed in the past to increase chemical resolution. Short chromatography times lead to high levels of co-elution, and ion mobility spectra are key to resolve them. For the first time, BSS techniques are used to deconvolve samples of the gas chromatography - ion mobility spectrometry tandem. We propose a method to extract spectra and concentration profiles based on the application of MCR in a sliding window. Our results provide clear concentration profiles and pure spectra, resolving peaks that were not detected by the conventional use of MCR. The proposed technique could also be applied to other hyphenated instruments with similar strong co-elutions.

Keywords: Blind Source Separation; Multivariate Curve Resolution; Ion Mobility Spectrometry; Gas Chromatography; Hyphenated instrumentation; SIMPLISMA; coelution

1. Introduction

Ion Mobility Spectrometry (IMS) is an analytical technique for characterizing chemical substances based on the velocity of gas-phase ions in an electric field [1]. Ion mobility spectrometers are able to detect trace levels of volatile chemicals with high-speed analysis and moderate selectivity. They are also portable enough to be commercialized as handhold instruments, being a recent research interest its miniaturization [2], [3]. IMS was first used in the 1970s for explosives and chemical warfare agents detection in military applications [4]. Over the past twenty years, IMS fields of application have widened and it is currently being used in environmental [5], industrial [6], and biomedical studies [7], drug detection [8], security applications [9], food quality [10] and fraud detection [11].

To improve IMS chemical resolution, it has been proposed to couple a multi-capillary chromatographic column (MCC) to pre-separate the chemical compounds of the sample [12], enabling the analysis of more complex samples. However, as MCCs are characterized by presenting short chromatography times, multiple compounds may still elute from the column at the same time. This effect is known as co-elution. Ion mobility spectra are therefore key to resolve these co-eluted chemicals.

Blind Source Separation (BSS) techniques, also named in chemometrics “resolution techniques”, are commonly applied to hyphenated analytical techniques that provide second order data. In IMS samples, the compounds' original concentration profiles and pure spectra can be deconvolved from the sample using BSS techniques [13]. For the first time, we propose a blind source separation technique in MCC-IMS data. Direct application of MCR techniques to full MCC-IMS data typically fails to resolve co-elution due to the complexity of the data and to the global noise which hinders the detection of weak but significant peaks. The typical approach in this case is the manual selection of the retention time window where the co-elution appears and the application of MCR in this data subset. However, in MCC-IMS chromatography conditions, co-elution is a prevalent phenomenon [14], [15]. Few individual peaks can be isolated in the total chromatogram and mostly very broad peaks are observed. To deal with this complexity, we propose an automatic manner to investigate co-elution across the whole chromatographic axis. The proposed method is able to detect and recover compounds in adverse co-elution conditions and reject spurious spectra with no physical meaning in an unsupervised manner.

The method is applied to real data corresponding to olive oil headspace analysis, with the aim to extract accurate concentration profiles and pure spectra for each sample. The extracted information can be used in a posterior step to discriminate among different regulated olive oil qualities in fraud prevention applications.

1.1 Ion Mobility Spectrometry

An IMS instrument consists of two main parts: an ionization chamber and a drift tube. Gas molecules enter the chamber and are ionized by a source (for instance radioactive, UV-lamp, corona discharge, electro-spray, among others) [16], [17]. The ionization processes take part at atmospheric pressure, being referred to as Atmospheric Pressure Chemical Ionization (APCI) [18]. Ionized molecules are prevented from entering the drift tube using an electrostatic grid, acting as an ion gate [19]. When the gate opens, ions are accelerated by an electric field through the drift tube, colliding with gas molecules and reaching a constant limit velocity. A collector at the end of the drift tube takes the charge from the ions producing a current and leaving neutralized molecules. The current provided by the collector can be interpreted as an ion mobility spectrum that lasts a few milliseconds. Components appear as peaks in the spectrum at different drift times, depending on their mass, shape and size [1].

The sample molecules are indirectly ionized by reactant ions if a radioactive source is used [1]. These ions are formed in the APCI process based on water chemistry reactions. The radioactive source ionizes nitrogen molecules that collide with water and other nitrogen molecules forming hydrated protons (H_3O^+). Depending on the atmosphere conditions, hydrated ammonium (NH_4^+) cations and hydrated superoxide (O_2^-) ions can also appear. The chemical substances in the sample are then ionized through collisions with the reactant ions. The remaining reactant ions form a peak -or several peaks- when they reach the detector. These peaks can be used as a reference and are usually known as the Reactant Ion Peaks (RIP).

Multi-Capillary Columns can be used to improve IMS's selectivity, at the expense of some of the IMS's portability and analysis speed [20]. A MCC is similar to a conventional chromatographic column, although it consists of a bundle of parallel capillaries that allow a higher flow rate of the carrier gas. The hyphenated instrument MCC-IMS is similar to conventional Gas Chromatography – Mass Spectrometry (GC-MS), as chromatography is used to separate the compounds, and spectrometry is used to identify them. However, GC-MS instruments offer a much higher resolution and powerful libraries for compound identification than MCC-IMS, but the later offers a portable solution, with lower costs and less maintenance requirements.

By continuously analyzing the output of the MCC with the IMS, the analysis of each sample produces a bidimensional matrix formed by consecutive measured spectra. The matrix dimensions are the MCC retention time and the IMS drift time.

1.2 Blind Source Separation techniques

Blind source/signal separation techniques are the collection of algorithms designed to estimate a set of source signals from measured mixtures. As mentioned in [21], techniques are blind because a) the source signals are not observed directly, b) the mixing matrix is unknown and c) no information is available about the composition of the mixture, not even the number of source signals present. These techniques are commonly used in signal processing [22] and are increasingly being used in chemical instrumentation applications [23], such as the analysis of nuclear magnetic resonance data [24], chemical reaction monitoring [25] and Raman spectroscopy [26]. BSS has been recently used to enhance information extraction from temperature-modulated metal oxide gas sensors [27] and to separate interferences from ion activity in ion-sensitive field-effect transistors [28].

As deconvolution problems are under-determined by definition, constraints are required to narrow the space of solutions. For many applications, Independent Component Analysis (ICA) [29] is an appropriate and successful technique if mixing models can be assumed to be linear and source signals to be statistically independent. However, in chemical analysis and specifically in IMS, statistical independence of compounds is not necessarily fulfilled [13]. Therefore other approaches are used to constrain the range of possible solutions [23] being Non-negative Matrix Factorization (NMF) techniques [30] and in particular Multivariate Curve Resolution (MCR) methods [31] common alternatives.

1.3 Multivariate Curve Resolution Alternating Least Squares

Multivariate Curve Resolution Alternating Least Squares (MCR-ALS) [32] assumes a linear decomposition of the mixing matrix, which can be written as shown in Eq. 1.

$$D = CS^T + E \quad (1)$$

D (*MxN*) is the measured mixing matrix, with *M* spectra of length *N*. *C* (*MxK*) is the abundances or concentrations matrix, that contains the proportions of each unmixed spectrum in the measured matrix and *S* (*NxK*) is the pure (or unmixed) spectra matrix that contains the *K* pure spectra of length *N*. *E* is a matrix of residuals (*MxN*).

Given an initial estimation of K pure spectra, MCR-ALS proceeds as follows:

1. Filter noise from the mixing matrix: First, compute PCA scores and loadings from the D mixing matrix. Then reconstruct a filtered version of D, named D*, using the first K principal components of the computed scores and loadings.

2. Estimate the concentration profiles using least squares:

$$C = \text{argmin}_C \, \| D^* - CS^T \|^2 \quad (2)$$

3. Impose constraints on the concentration profiles

4. Estimate the pure spectra using least squares:

$$S = \text{argmin}_S \, || D^* - CS^T ||^2 \quad (3)$$

5. Impose constraints on the pure spectra
6. Iterate steps 2-5 until convergence.

The key to obtaining reliable concentration profiles and pure spectra depends on the estimation of the number of components in the mixture, the initialization of the pure spectra and the imposition of constraints.

The number of components for each window can be estimated with several methods such as [33]–[35]. However, a simpler approach described in [36] is commonly used: the number of components is determined as the number of singular values of the matrix above a given threshold, representative of the noise in the sample.

There are multiple ways of obtaining an initial estimation of the pure spectra, being SIMPLe-to-use Interactive Self-modeling Mixture Analysis (SIMPLISMA) [37] and Evolving Factor Analysis (EFA) [38] the most common ones. Although EFA works well on samples presenting unimodal concentration profiles, on IMS this condition does not necessarily hold, making SIMPLISMA the most common alternative in this field [13], [39].

Many constraints can be imposed on the concentration profiles and pure spectra depending on the prior knowledge of our particular problem: On IMS spectra, non-negativity can be imposed on both concentration profiles and spectra. Moreover, as the ionization process consists in a charge transfer from the RIP to the compounds, charge conservation can be imposed on the concentration profiles (closure on *C*). Unimodality constraints are not suitable for concentration profiles, but can be imposed to the resolved spectra shapes. Finally, selectivity constraints to the concentration profiles can also be imposed if some components are known to appear at a particular retention time range.

The MCR-ALS algorithm is based on a least squares minimization of the global error of the factorization. As it is shown in our results, local peaks with low intensities appearing in regions with strong co-elution may pass unnoticed by MCR-ALS, as they present a contribution to the error comparable to or smaller than the global noise of the sample. In these cases, increasing the estimated number of components in the mixture leads to extracting spurious compounds with no physical meaning instead of the desired local compounds.

1.4 Proposed technique: Sliding Window Multivariate-Curve Resolution

In order to overcome the limitation in resolving low intensity peaks when the conventional MCR-ALS is applied to the whole MCC-IMS data matrix, we propose to apply MCR in short partially overlapped windows, slicing the matrix in the retention time axis. In addition, window overlap is imposed to avoid splitting peaks on window borders and to avoid detecting spurious compounds inconsistent across windows.

First, the initial estimations of pure spectra and concentration profiles are obtained by applying SIMPLISMA to each window. By using SIMPLISMA in this fashion, we can extract local peaks with low intensities, as they have comparatively higher peak purity within a single window. The number of components for each window is estimated using the threshold on singular values previously described in Section 1.3. To select the threshold, the singular values were plotted in decreasing order (plot not shown), presenting the typical elbow-like shape. The threshold was selected when the singular values begin to stabilize. Given the initial estimations, we use MCR-ALS to extract a set of concentration profiles and pure spectra for each window.

Finally, the results from all the windows are merged into a single set of concentration profiles and spectra representative of the whole sample. To do so, compounds are tracked through consecutive windows based on the similarity of their spectra. The angle between two pure spectra s_i and s_j is computed as shown in Eq. 4.

$$\theta_{i,j} = \arccos\left(\frac{s_i \cdot s_j}{|s_i||s_j|}\right) \quad (4)$$

Fig. 1 shows a diagram with an example of four compounds being tracked along three windows. The link between two spectra of consecutive windows is formed only if their angle is below a given threshold. In this figure, compounds C1 and C2 are being tracked along all the windows (N to N+2) while compound C3 disappears on window N+1 because no link can be established on window N+2. Compound C4 does not appear until the N+1 window. The last spectrum in window N+1 does not establish any link, thus it is considered spurious and is rejected from the final set of tracked compounds.

Windows are highly overlapped to guarantee that if no link can be established for a spectrum, then it can be safely considered as spurious and rejected from the final set. The final estimation of the pure spectra for each compound is computed as the mean of all the tracked spectra. The standard deviation of the mean is used as its error estimation. Averaging and computing the standard deviation are used likewise to obtain the final estimation of the concentration profiles.

2. Materials and Methods

2.1 Description of the samples

The proposed technique was applied to the olive oil dataset described in [10]. Current regulations in the European Union classify olive oils in three different categories according to their quality, namely Extra Virgin Olive Oil (EVOO), Virgin Olive Oil (VOO) and Lampante Olive Oil (LOO), being EVOO the category of highest quality and LOO the lowest one. This classification is based on several chemical parameters (free acidity, peroxide value and Ultra-violet absorbance) and a sensorial analysis. A proper control of olive oil qualities is crucial, not only because of the difference in price but also because LOO is not suitable for human consumption without being previously refined.

Ninety-eight olive oil samples from different qualities (27 samples of LOO, 28 samples of VOO and 43 samples of EVOO) were obtained from the Agrarian Laboratory of Junta de Andalucía and an oil press from Córdoba (Spain) during the 2009-2010 and 2010-2011 harvests. In order to keep the organoleptic features of the samples, they were stored at 4ºC until their analysis.

2.2 Analytical methods

Samples were analyzed with a MCC-IMS instrument (FlavourSpec®) from Gesellschaft für analytische Sensorysteme mbH (G.A.S), Dortmund (Germany). The olive oil headspace was directly sampled with a heated splitless injector, and the instrument was coupled to an automatic sampler unit (CTC-PAL, CTC Analytics AG, Zwingen, Switzerland) to improve reproducibility.

One gram of sample was placed in a 20-mL vial that was closed with magnetic caps. Samples were incubated at 60ºC for 10 minutes and 100 μL of sample headspace was automatically injected into the injector (80ºC) of the MCC-IMS.

The carrier gas going through the injector inserted the sample into the chromatograph, previously heated to 30ºC for pre-separation on a non-polar OV-5 MCC (20 cm long, ~1000 parallel glass capillaries, filled with 5% diphenyl and 95% dimethylpolysiloxane). The analytes were eluted in an isothermal mode and driven into the IMS.

Inside the IMS, the ionization was produced with a Tritium source (6.5 keV). Ions entered the 6 cm long drift tube operating at a constant electric field of 350 V/cm and at a temperature of 60ºC. Spectra were acquired in the positive ion mode, generating each spectrum with the average of 32 scans, using a grid pulse width of 100 μs. The IMS sampled at 150 kHz and each scan lasted 20 ms. Each spectrum is 3000 points long.

Each sample was analyzed for 15 minutes, obtaining a complete IMS spectrum every 0.7 seconds. Compounds only eluted during the first 4 minutes of the retention time, leading to 340 spectra with information per sample. Each sample can be represented by a 340x3000 matrix.

2.3 Pre-processing

Noise present in each spectrum of the sample was filtered using a second order Savitzky-Golay filter [40] with a window size of 13 data points. The window size was selected assessing that the RIP height distortion caused by the filter was smaller than 1% of its non-filtered maximum value.

Next, a baseline was estimated and subtracted from the spectrum: the estimation of the baseline was computed by fitting a 4^{th} order polynomial to two non-peaked (empty) regions in the spectrum found in the regions 1-5 ms and 14.7-18.7 ms.

Finally, only the drift time region from 4 ms to 14.65 ms (1600 sampled points) contained information, so irrelevant regions were cropped out. Each sample was therefore reduced to a 340x1600 matrix.

2.4 Sliding Window MCR

The proposed Sliding Window MCR (SW-MCR) technique is applied to the sample, using a window length of ten spectra (7 seconds) and a window shift of a single spectrum (0.7 seconds). The window length was selected based on the typical width of a peak in the chromatogram, computed as the median full width at half maximum (FWHM) of ten representative peaks in the sample.

Larger window sizes and smaller window overlaps may be used to reduce the computational cost of the method. A larger window size would imply that more compounds can be found in the same window. If the window is too large we will face the same problem than with conventional MCR-ALS application: we may fail to detect local peaks with low intensities. Regarding the window overlap, if the window overlap is too small this would increase our chances of splitting peaks in window borders and would hinder our ability to distinguish spurious solutions from actual compounds, as actual compounds would not have to necessarily appear among consecutive windows anymore.

After inspecting the distribution of singular values along the windows, we set a threshold to determine the number of components. Data not represented by the selected components was discarded using a PCA filter.

Regarding the MCR-ALS configuration, we initialized the pure spectra and the concentration profiles for each window using SIMPLISMA. We imposed the following constraints: 1) non-

negativity to both concentration profiles and pure spectra via fast non-negative least squares, 2) closure to the concentration profiles and 3) unimodality to the resolved spectra. Additionally, we imposed a selectivity constraint to improve the RIP pure spectrum estimation: given that at the end of the sample (high retention times) no compounds elute from the column, the only compound present in the latest spectra is the RIP. From a blind source separation perspective, this information is very valuable, as an accurate estimate of the RIP pure spectrum can be easily obtained.

Finally, in order to track the resolved spectra through the windows, an angle threshold of 15 degrees was used. This angle was chosen after inspecting the angle distribution of the pairwise comparison of the spectra.

3. Results and Discussion

A selected informative region of an olive oil sample can be seen in Fig. 2. The Reactant Ion Peak can be seen close to 6 ms in drift time along all the retention time range. There are multiple peaks in the same retention time range, indicating a strong co-elution of the components. As peaks are created by the transference charge from the reactant ions, the RIP intensity decreases at the retention time when other peaks appear in the ion mobility spectrum. At higher retention times the RIP recovers all the charge returning to a constant intensity as no more compounds elute.

The intensity of the RIP can be used as a non-selective measure of the global elution of compounds. Integrating the RIP (from 6.26 ms to 6.6 ms) and subtracting it from the maximum intensity, we obtain the charge that has been transferred to other compounds throughout the retention time. This figure of merit is called the "Reverse RIP" and it is analogous to a total ion chromatogram in gas chromatography - mass spectrometry samples. Fig. 3 shows the reverse RIP of an olive oil sample. The reverse RIP shows a continuous elution of compounds along approximately the first minute of the sample.

The performance of the proposed SW-MCR method has been assessed by comparing the extracted concentration profiles and pure spectra with the ones resolved using conventional MCR-ALS on the whole sample, using the same described pre-processing and imposing the same constraints. Regions with strong co-elution are of particular interest, as for those regions conventional MCR-ALS is not able to resolve all compounds, especially the smallest ones. 22 peaks of the first 100 seconds of the sample were randomly selected (covering higher and lower peak intensities) and we checked the retention time range where each peak had been detected by each method. Table 1 shows the actual retention time range of the sample and the one obtained by each method. When the peaks are detected, there is considerable agreement between both methods; however MCR-ALS failed to detect 9/22 of the analyzed peaks.

Fig. 4 shows a sample region with co-elution and peak intensities of different magnitudes: at retention time 40 s two peaks appear: a peak of 2200 intensity units at drift time 10 ms and a less intense peak of 650 intensity units at 7.8 ms. Close to 50 s a third peak of 230 intensity units appears at 8.7 ms. The difference of the peak intensities is almost of one order of magnitude.

Using MCR-ALS in the whole sample, the resolved pure spectra and concentration profiles on the described region are shown in Fig. 5. The only meaningful compound extracted at that retention time region apart from the RIP is the most intense one, found at 10 ms and marked using a wider line. Other compounds appear, some of them can be interpreted as tails or replicas of the 10 ms peak, but they provide no particular meaning so they must be discarded as spurious compounds. Additionally, the concentration profile for the resolved peak shows non-zero concentration in the 20-40 second retention time region, before the compound has eluted.

When using SW-MCR, the pure spectra and concentration profiles for the three peaks on the described region are extracted (see Fig. 6). The computed error bars of the pure spectra and concentration profiles show a high consistency among different window estimations. As expected, the concentration of the largest peak (at 10 ms) is similar to the concentration resolved using MCR-ALS. The peak with lowest intensity (at 8.7 ms) is well resolved too, with a concentration profile one order of magnitude smaller than the largest peak, as expected. The medium intensity peak (at 7.8 ms) is also detected, although its tracking is interrupted in the 47-53 seconds range. This shows a limitation of the proposed technique: Peaks with a constant intensity in the whole window cannot be detected by SIMPLISMA because the standard deviation of the peak maximum along the window is zero leading to zero purity values. However, the peak is tracked again in further windows once the intensity varies again.

The SW-MCR technique allows extracting detailed information of the co-elution present in the sample. Fig. 7 shows the distribution of the resolved compounds along the retention time. Each row represents a tracked compound, showing the retention time region in which it has been detected and deconvolved. For instance, the first row represents the RIP, which is tracked along all the chromatogram. Fig. 2 and Fig. 3 showed multiple compounds co-eluting from the column on the first seconds of the analysis. Fig. 7 confirms that SW-MCR is able to detect them, resolving more than 6 compounds on a single window. As the retention time increases, Fig. 2 shows less peaks co-eluting, and this is reflected on Fig. 7 as the compound overlap decreases. On the first 100 seconds of the sample, SW-MCR was able to track up to 46 compounds revealing the richness of information present in the MCC-IMS samples.

The estimated concentration profile of the RIP is shown on Fig. 8. Retention time regions with lower RIP concentrations indicate regions with intense peaks, or regions with multiple peaks

detected, where (almost) all the charge has already been transferred. The recovered concentration profile for the RIP can be compared with the extracted reverse RIP shown in Fig. 3. Fig. 8 peaks can be matched with Fig. 3 valleys, proving the consistency of our technique.

The angle threshold used for tracking the compounds rejects spurious peaks that appear on a single window. Fig. 9 shows the estimated number of components using singular value decomposition and the actual number of tracked components for a particular window. Regarding the number of tracked components, all windows are able to track the RIP and therefore the number of tracked components is always greater than or equal to one compound. Most of the windows had none or one spurious compound, although some windows had up to five spurious components which were rejected. This rejection allows us to use lower thresholds on the singular value decomposition, as overestimations in the number of components of a window are regulated in the peak tracking step. Lower thresholds on the singular values allow us to detect peaks close to the noise level, as they are consistent across different windows and are not rejected.

Regarding the computational cost of the technique, most of the computing time is spent on the MCR-ALS optimization, as it is an iterative algorithm. For the conventional MCR-ALS, up to 30 iterations are required to reach convergence. For the proposed SW-MCR a maximum of 10 iterations per window were used although for most of the windows 5 iterations were enough for MCR-ALS to converge. In any case, the most expensive part is the (non-negative) least squares estimation required on each concentration profile and pure spectrum estimation. On a 2013 workstation computer with an Intel i7 processor, the conventional MCR-ALS method takes 4.5 minutes to extract the concentration profiles and pure spectra from the sample. This process cannot be parallelized due to its iterative nature. The proposed SW-MCR method requires 1.75 seconds per window. Given that there is a strong window overlap, the overall cost per sample sums up to 22 minutes. Even though the global time is higher, the SW-MCR method is well suited for parallelization, as each window is independent from the others. For our case, with a window shift of 0.7 seconds, three CPU cores would be needed for a real time application, unfeasible with the conventional algorithm.

4. Conclusions

A novel technique for improved chemometric resolution of gas chromatography ion mobility spectrometry samples has been presented, showing for the first time that blind peak deconvolution techniques can be successfully applied to this analytical hyphenated instrument.

The proposed technique has been tested on olive oil headspace samples. The samples analyzed present a strong co-elution of the individual chemical components, as shown by the wide peaks in

the reverse RIP ion chromatogram. Co-eluting peaks are not properly resolved using conventional MCR-ALS methods, as peaks of lower intensities cannot be discriminated from the sample noise. Additionally, spurious compounds appear requiring supervision of the results.

Using the proposed SW-MCR method, we were able to deconvolve the pure spectra and concentration profiles of most of the peaks, even the ones with lower intensities, rejecting spurious solutions automatically.

The computational cost of the proposed technique is higher than the cost of the conventional MCR-ALS method, mainly because of the higher window overlap. However, our method can be easily parallelized, making our method more scalable and even suitable for real time applications.

Further work will be oriented to improving the initial estimation of the concentration profiles and pure spectra, in order to overcome the limitations in SIMPLISMA to resolve peaks of constant intensity along the entire window.

The proposed method has been applied to MCC-IMS samples, although we believe that it can be applied to other hyphenated instruments with similar strong co-elutions.

Acknowledgements

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Figures

Figure 1: Diagram of the tracking of spectra through three windows. Links between spectra are established if their angle is lower than a given threshold.

Figure 2: Region of a MCC-IMS olive oil sample. The Reactant Ion Peak (RIP) is observed at 6 ms. Multiple peaks on the same retention time indicate a strong co-elution. Note that both axes are reversed to prevent high intensity peaks from hiding the low intensity ones.

Figure 3: Reverse RIP. Analytes eluting from the column will show as a peak in the reverse RIP. The RIP is computed as the integral (from 6.26 to 6.6 ms) of each IMS spectrum and it represents the charge that has not been transferred to other analytes at a given retention time. The RIP's maximum represents the total charge available. By subtracting the charge that has not transferred to the total charge, the reverse RIP is obtained.

Figure 4: MCC-IMS region (top view). This region shows co-elution of different compounds: a section of the RIP found at 6.4 ms and three other compounds appear 7.8 ms, 8.6 ms (less intensely) and 10 ms.

Figure 5: Pure spectra and concentration profiles resolved by MCR-ALS. Thick line: main peak resolved. Dashed lines: tails and replicas of the resolved peak. Thin lines: spurious compounds.

Figure 6: Pure spectra and concentration profiles resolved by SW-MCR, deconvolving three co-eluting spectra. The small size of the error bars shows a high consistency among the tracked windows.

Figure 7: Tracked compounds along different windows. Each row represents a different pure spectrum. The first one is the RIP, which is being tracked along all the windows. This plot shows how co-elution of three and more components can be resolved at several retention times.

Figure 8: The extracted Reactant Ion Peak using SW-MCR. The reverse shape of the concentration profile is comparable to the reverse RIP shown in Fig. 3.

Figure 9: Rejection of spurious compounds. In black: the number of tracked compounds for each window. In white: the initial estimation of the number of components using singular value decomposition. The difference of both black and white values is the number of rejected spurious compounds.

Tables

Table 1: Localization of 22 randomly selected peaks from the sample, on MCR-ALS and on SW-MCR deconvolution. The retention time ranges are in agreement on the detected peaks, however MCR-ALS was unable to extract 9/22 peaks.

Table 1

Table 1

Peak #	Drift time (ms)	Max. intensity (a.u.)	Retention time range (s)		
			Sample	MCR-ALS	SW-MCR
1	6.45 (RIP)	3951	All	All	All
2	7.30	3936	1-4	0-10	0-4
3	7.60	1002	3-7	2-7	3-9
4	7.75	400	4-10	NF	4-9
5	8.30	782	5-9	4-8	4-10
6	9.10	177	5-12	NF	4-10
7	8.10	695	4-9	0-20	4-10
8	8.78	731	5-12	4-12	5-12
9	8.60	623	4-12	4-7	5-13
10	7.15	474	4-13	3-7	5-15
11	8.90	2100	8-13	8-12	8-13
12	8.10	425	11-19	NF	12-20
13	6.75	490	11-23	NF	12-23
14	10.30	1190	20-27	22-27	21-27
15	7.20	188	21-29	NF	21-28
16	8.20	481	21-32	NF	21-31
17	8.50	390	30-38	30-35	30-37
18	7.80	317	28-40	NF	30-40
19	7.30	445	31-40	NF	32-40
20	9.90	2200	40-55	40-60	40-50
21	8.70	220	50-63	NF	50-56
22	7.65	650	45-80	50-80	55-80

Figure 1

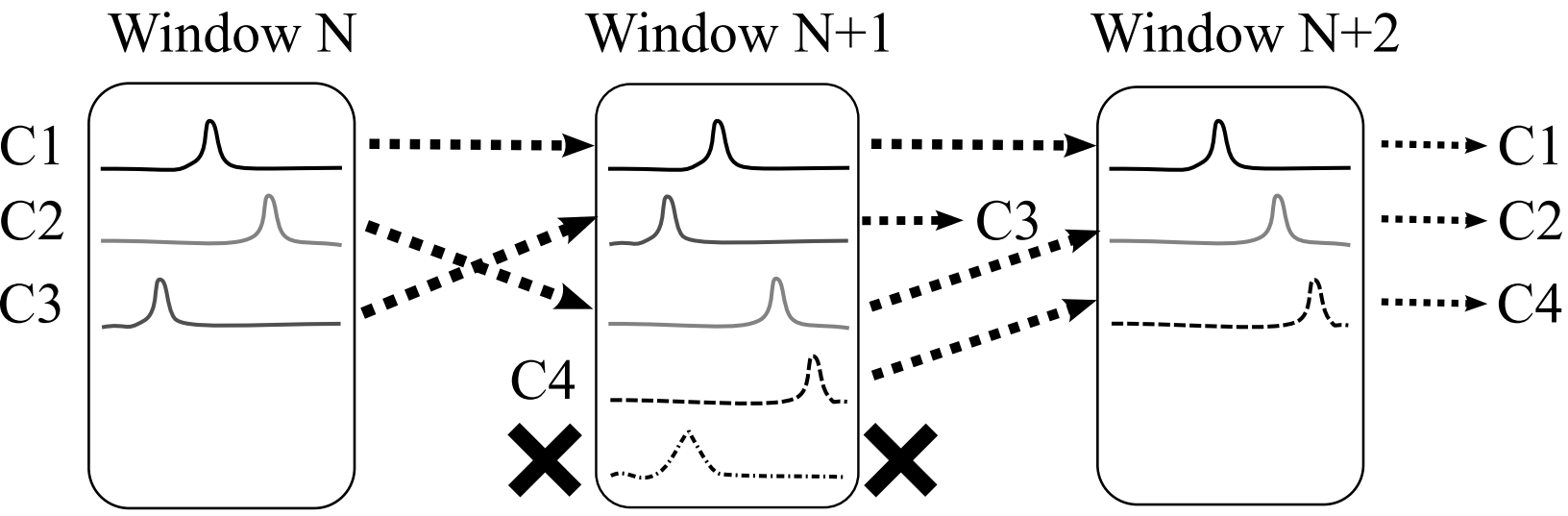
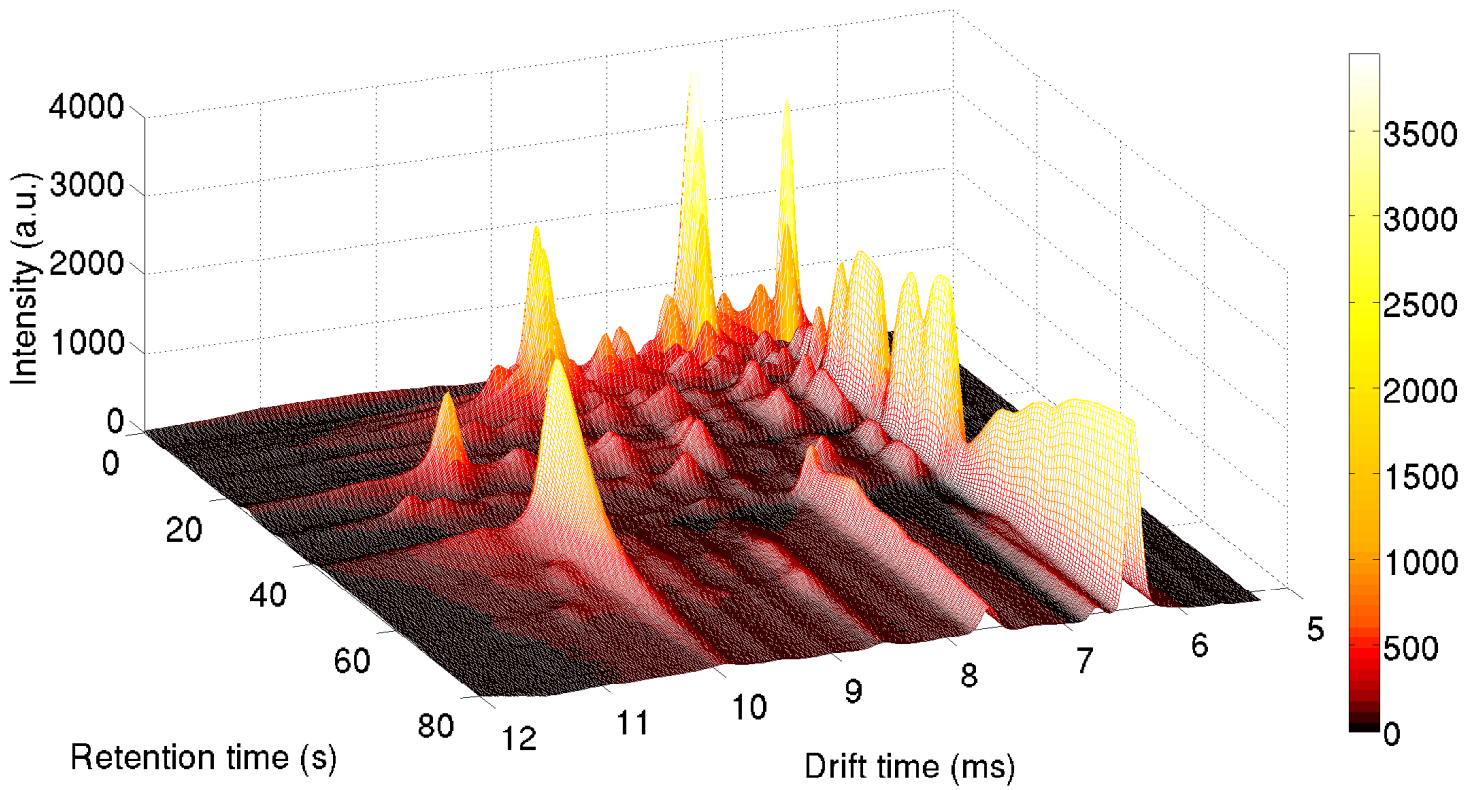


Figure 2 (Color)



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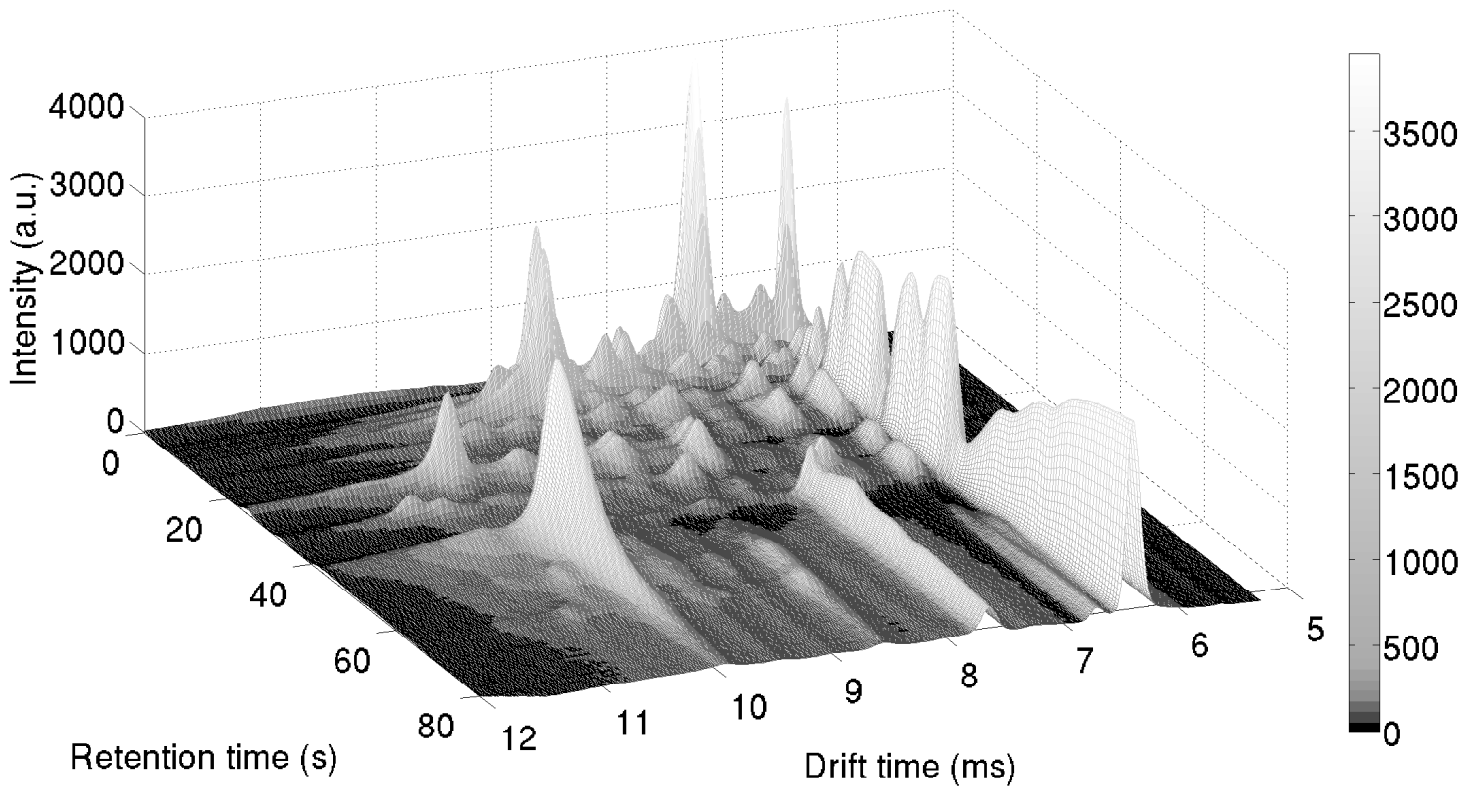

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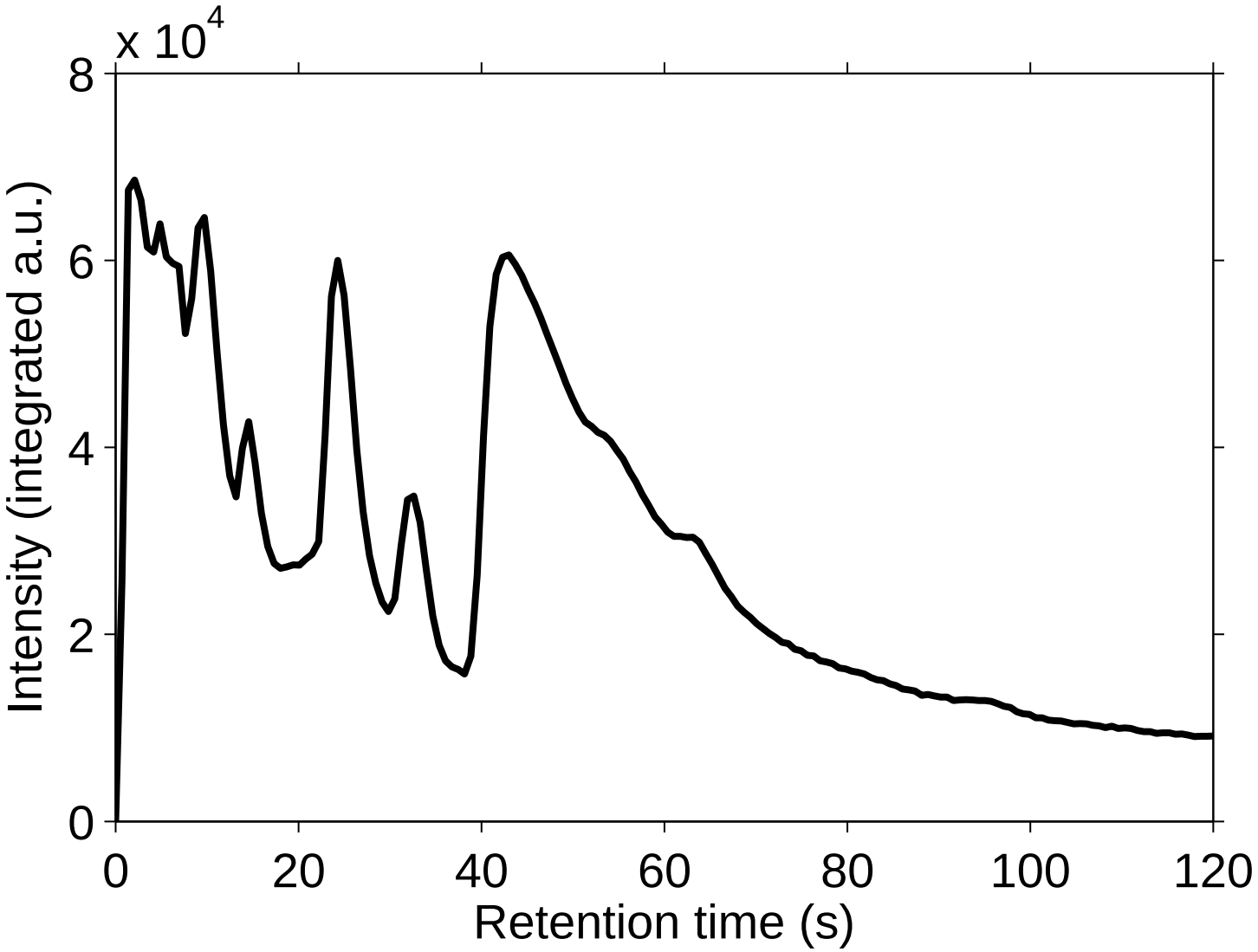
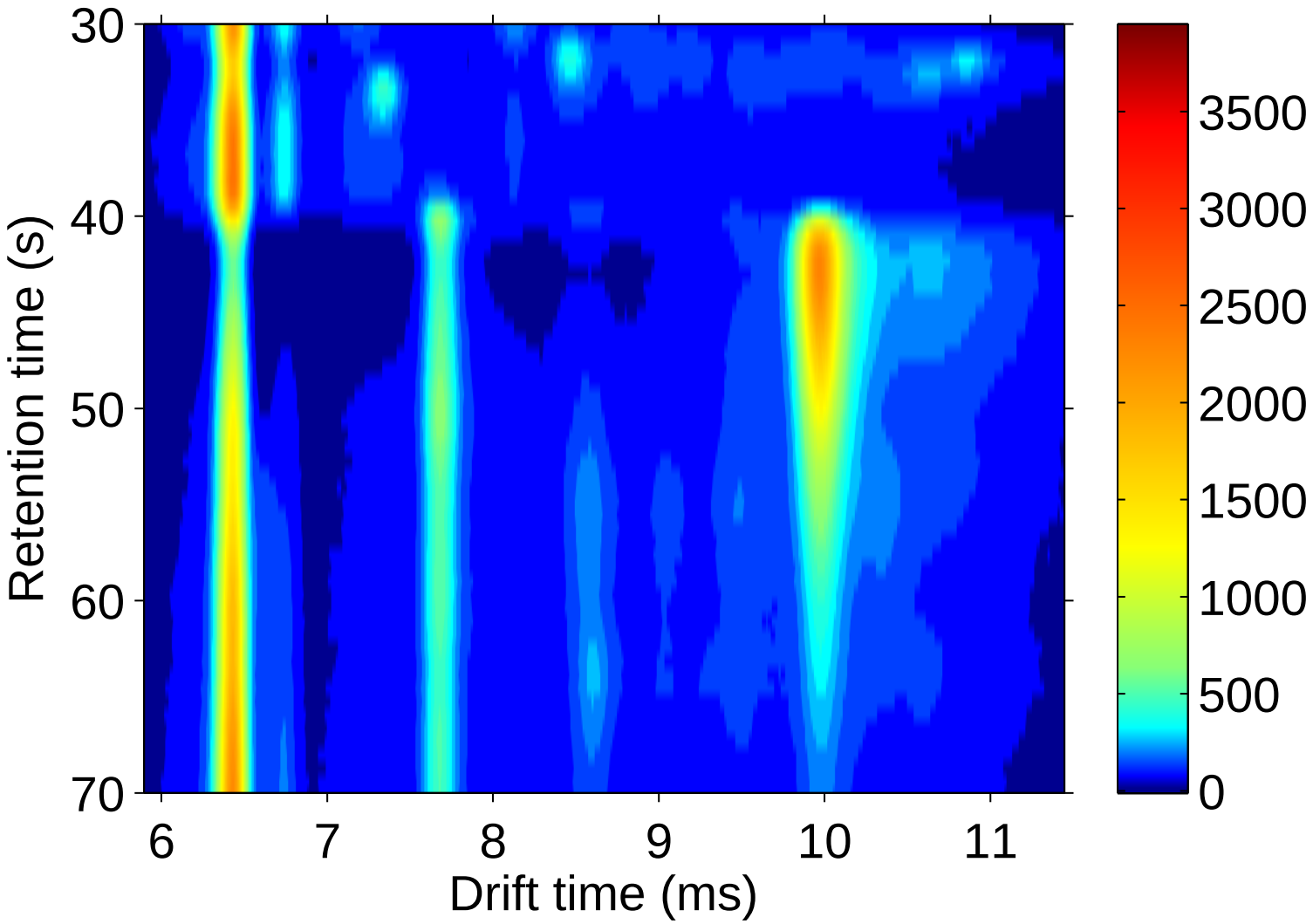

x 10^4
8
6
4
2
0
Intensity (integrated a.u.)
0
20
40
60
80
100
120
Retention time (s)

Figure 4 (Color)



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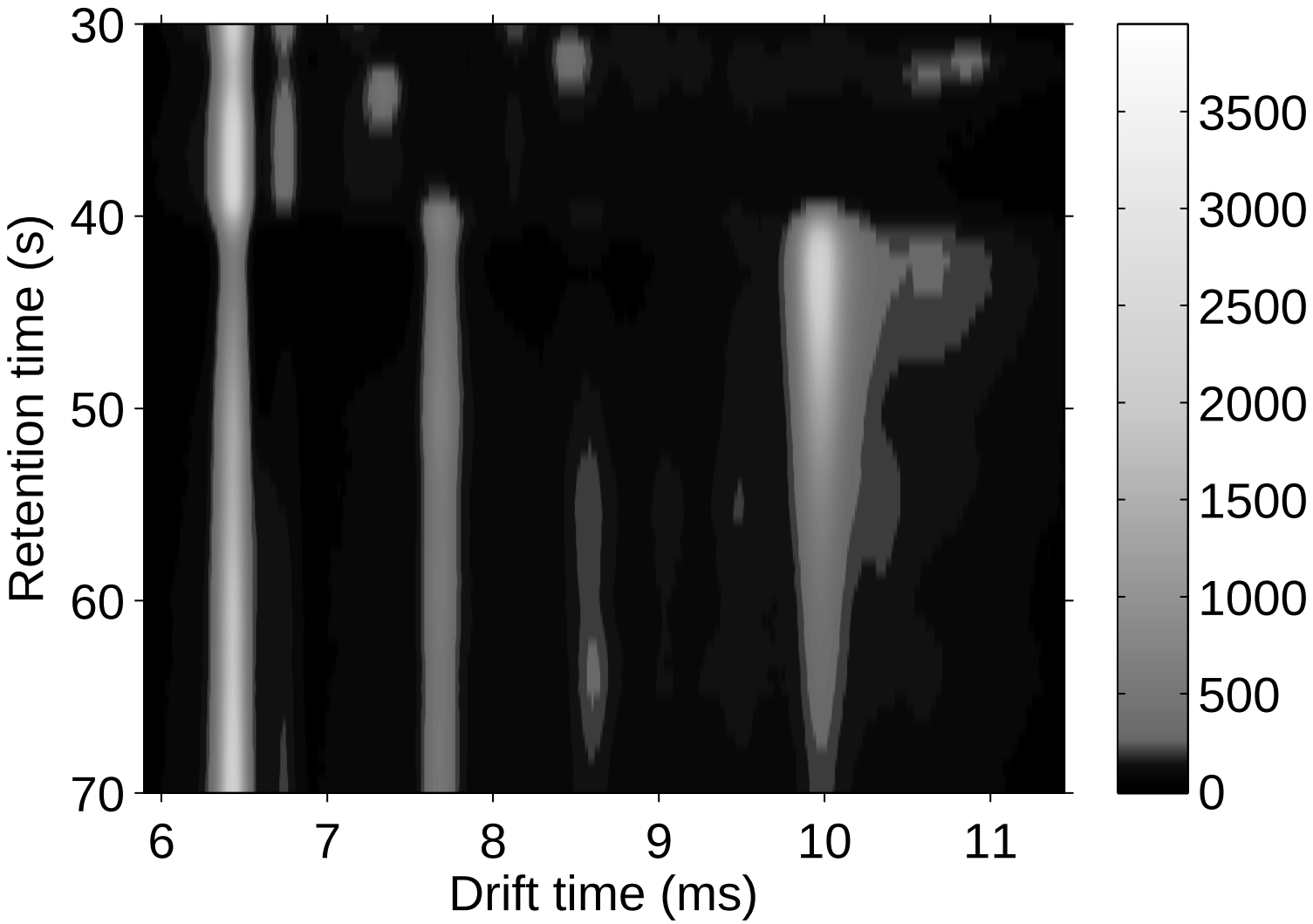


Figure 5

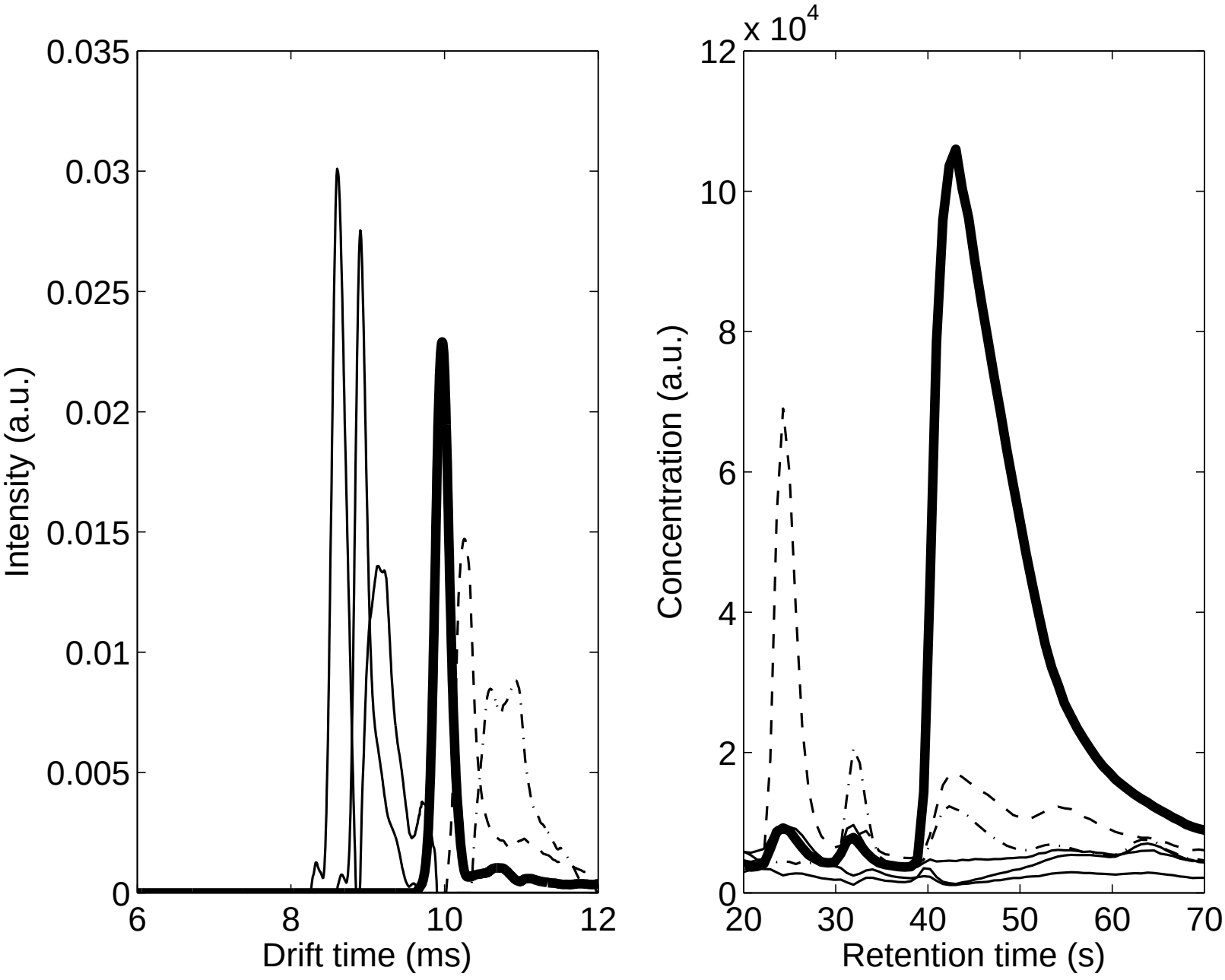

0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
Intensity (a.u.)
6
8
10
12
Drift time (ms)
x 10^4
12
10
8
6
4
2
0
Concentration (a.u.)
20
30
40
50
60
70
Retention time (s)

Figure 6

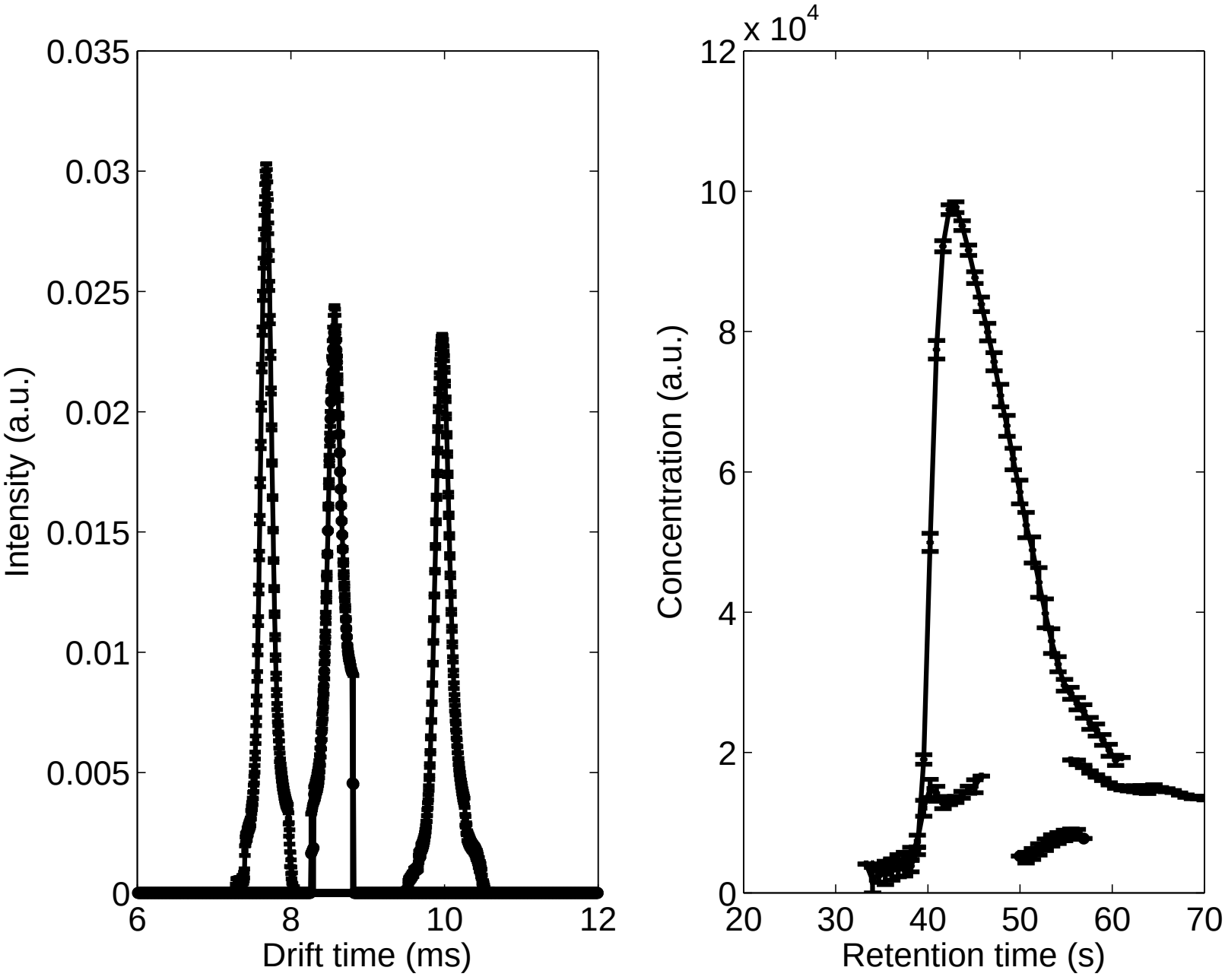

0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
Intensity (a.u.)
6
8
10
12
Drift time (ms)
x 10^4
12
10
8
6
4
2
0
Concentration (a.u.)
20
30
40
50
60
70
Retention time (s)

Figure 7 (Color)

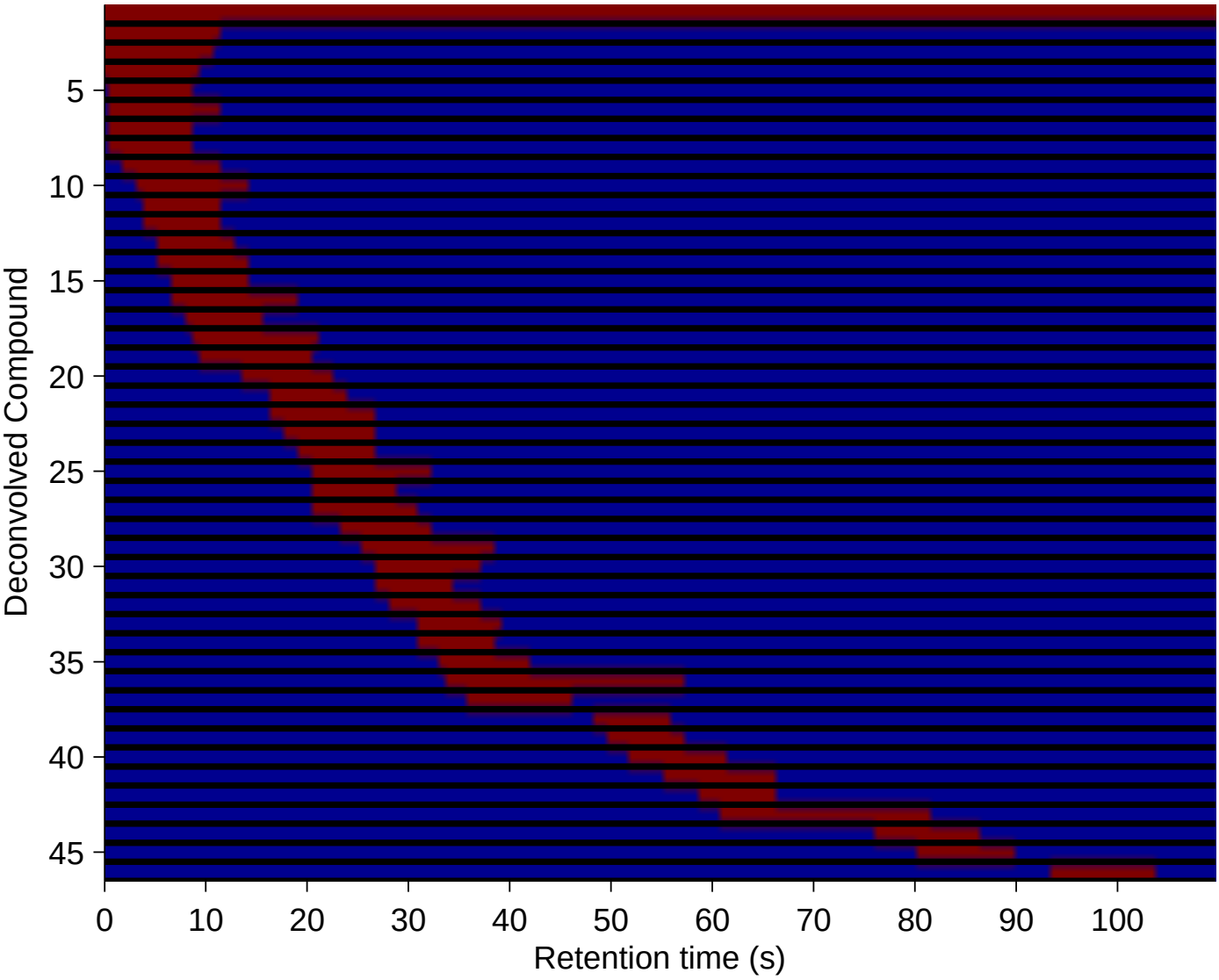


Figure 7 (Black and White)

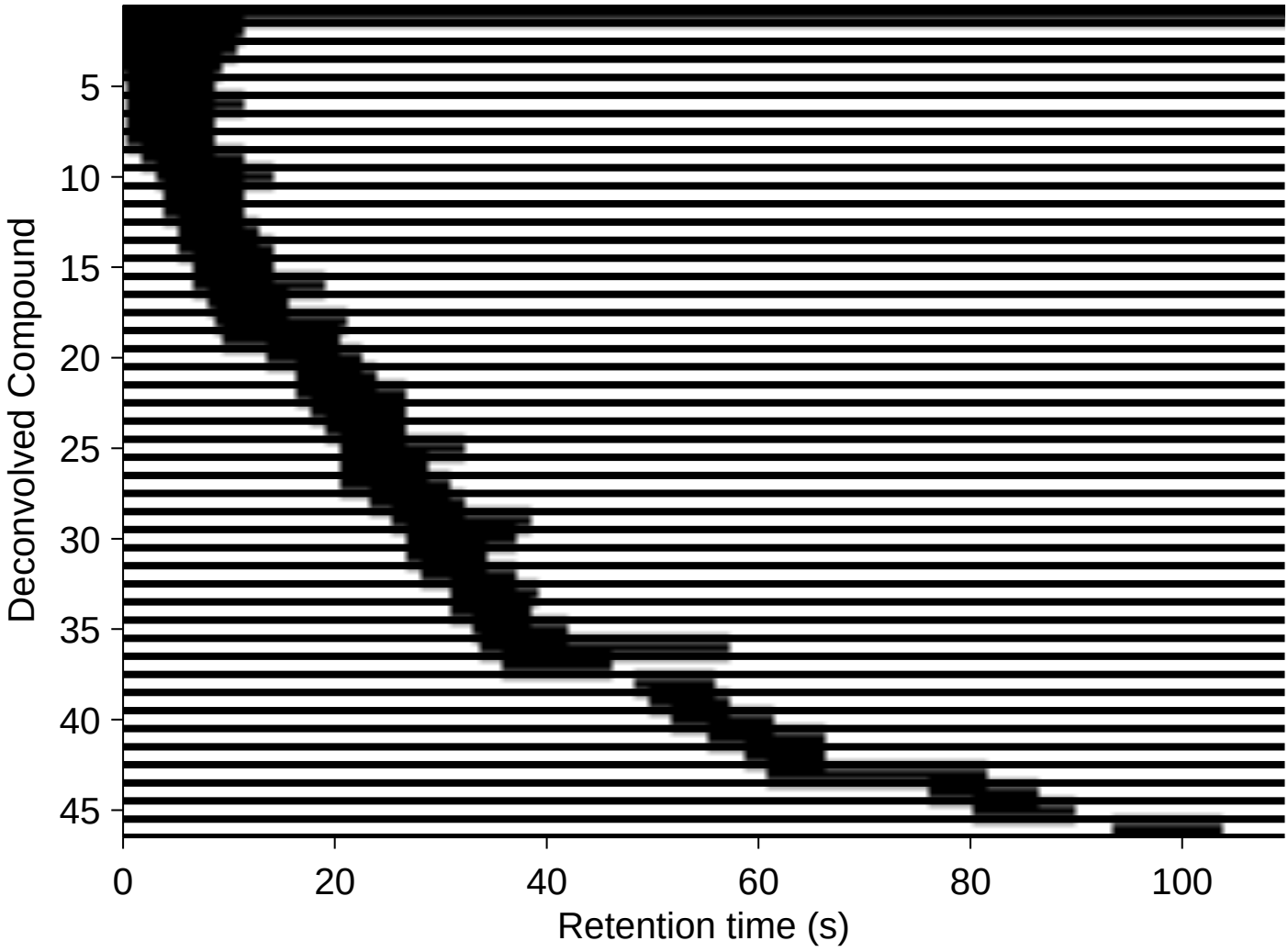


Figure 8

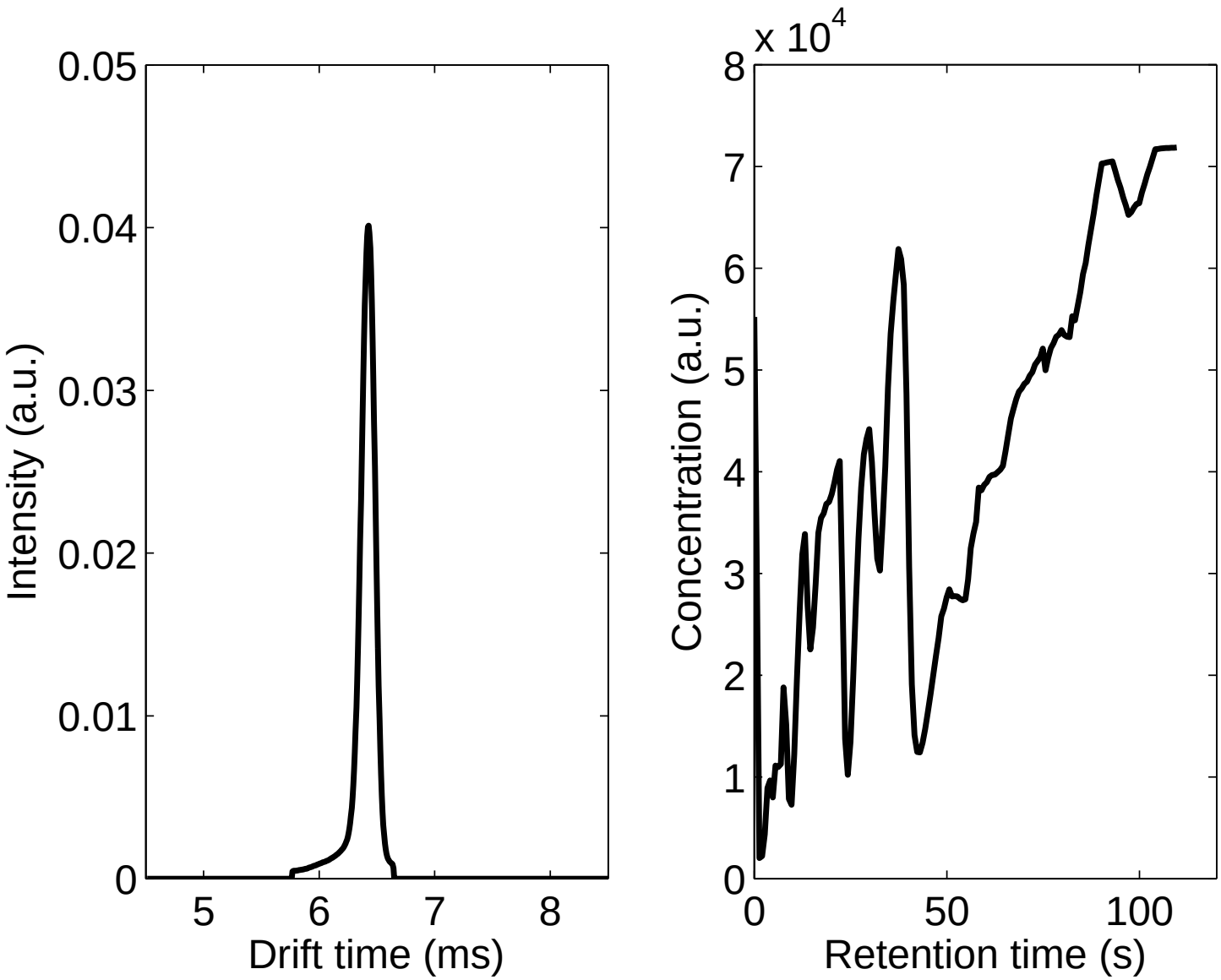
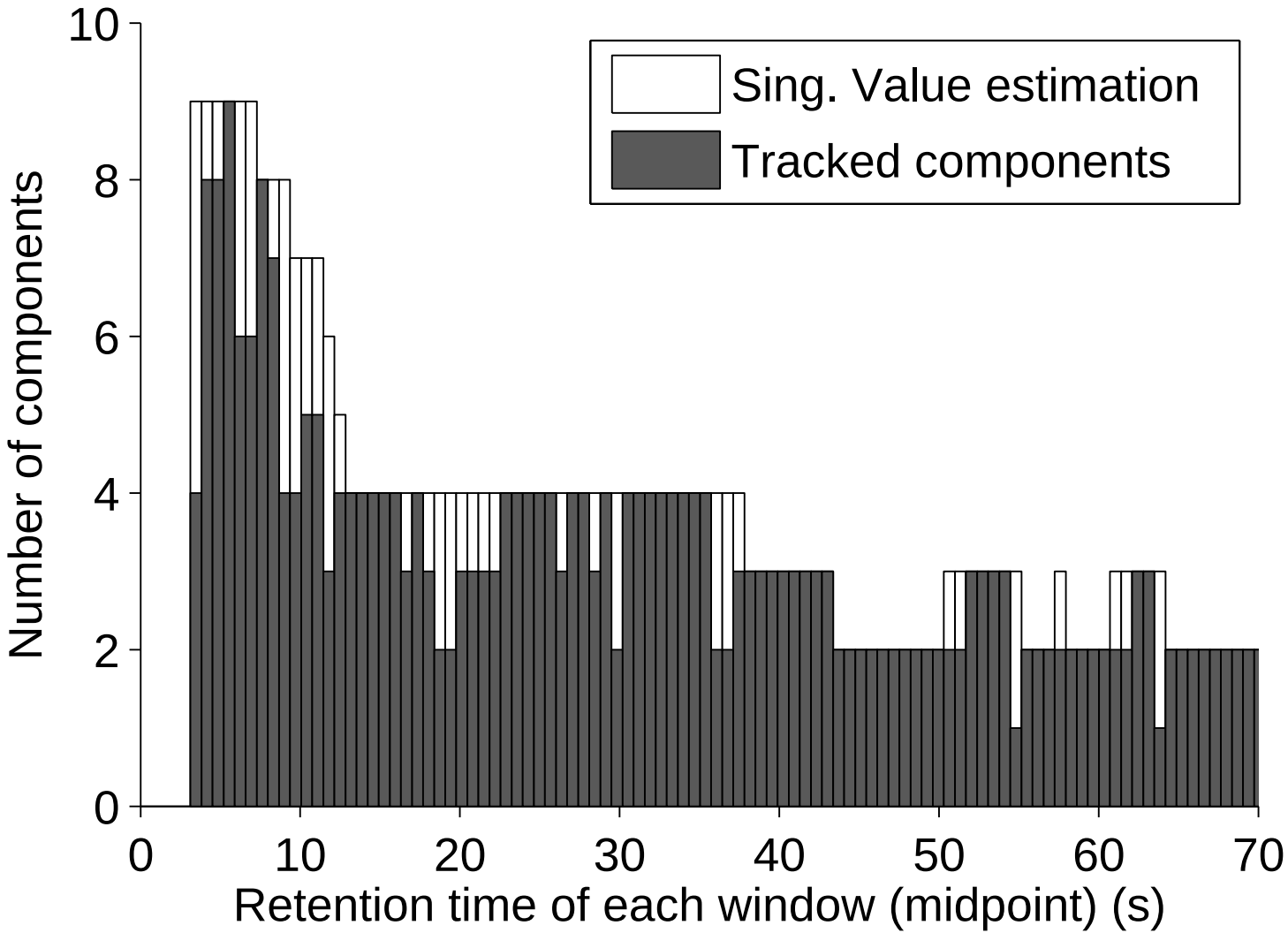

0.05
0.04
0.03
0.02
0.01
0
Intensity (a.u.)
5
6
7
8
Drift time (ms)
x 10^4
8
7
6
5
4
3
2
1
0
Concentration (a.u.)
0
50
100
Retention time (s)

Figure 9


Sing. Value estimation
Tracked components
Number of components
Retention time of each window (midpoint) (s)
0
2
4
6
8
10
0
10
20
30
40
50
60
70

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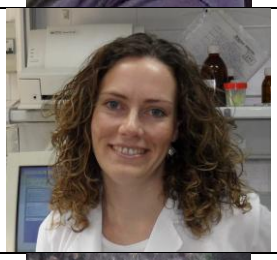
	Dr. Antonio Pardo (Barcelona, 1967) received his diploma in physics 1991 and his PhD in 2000 from the University of Barcelona. During his PhD studies he worked in system identification with applications in gas sensor systems. Since 2005 he is associate professor in the Departament d'Electrònica at Universitat de Barcelona. He has been involved in several scientific and technologic projects as a researcher and as coordinator, in which the chemical instrumentation has a key role. His research interests include signal processing for gas sensors and pattern recognition as well as hardware and software developments for artificial olfaction.
	Rocío Garrido Delgado got her Master's Degree in Chemistry at the University of Córdoba (Spain) in 2007. Since then, she joined at Analytical Chemistry department at the University of Cordoba working with Ion Mobility Spectrometry. She presented her Doctoral Thesis in November 2011. Currently she continues developing her research in the Prof. Miguel Valcárcel group.
	Lourdes Arce obtained her Master's Degree in Chemistry from the University of Córdoba (Spain). She obtained her PhD in Sciences in 1999. Since 2007, she is associate professor in the Analytical Chemistry Department at the University of Córdoba. Her main research project is devoted to the "Development and application of vanguard (Ion Mobility Spectrometry)-rearguard (Capillary Electrophoresis, Gas Chromatography, etc.) new metrology analytical strategies". Current research is directed towards the pursuit of studying the potential of IMS and CE in the agro-food and forensic field.

Dr. Santiago Marco completed his university degree in Applied Physics in 1988 and received a PhD in Microsystem Technology from the University of Barcelona in 1993. He held a European Human Capital Mobility grant for a postdoctoral position at the Department of Electronic Engineering at the University of Rome "Tor Vergata". Since 1995, he is Associate Professor of Electronic Instrumentation at the Department of Electronics at the University of Barcelona. In 2004 he had a sabbatical leave at EADS-Corporate Research, Munich, working on Ion Mobility Spectrometry. In 2008 he was appointed leader of the Signal and Information Processing for Sensing Systems Lab at the Institute of Bioengineering of Catalonia. His research concerns the development of signal/data processing algorithmic solutions for smart chemical sensing based in sensor arrays or microspectrometers integrated typically using Microsystem Technologies (more at http://www.ibecbarcelona.eu/signalinfo).