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Novel system for classifying chromatographic applications, exemplified by comprehensive two-dimensional gas chromatography and multivariate analysis

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Abstract

For practical chromatographers it is extremely difficult to judge the merits and limitations of new technological developments. On the other hand, it is nearly impossible for those at the forefront of technology to judge the implications of their efforts for all specific applications of chromatography. Both chromatographers and researchers can be aided by a classification of the numerous specific applications into a few well-defined categories. In this paper, we propose such a classification of all chemical analysis by chromatography into three generic types of applications, viz. target-compound analysis, group-type separation, and fingerprinting. The requirements for each type are discussed in general terms. The classification scheme is applied to assess the benefits and limitations of comprehensive two-dimensional gas chromatography (GC×GC) and the possible additional benefits of using multivariate-analysis (MVA) techniques for each type of application. The conclusions pertaining to the generic types of applications are indicative for the implications of new developments for specific chemical analysis by chromatography.

Keywords: Classification; Generic applications; Target-compound analysis; Group-type separation; Fingerprinting; GC×GC; Multivariate analysis

1. Introduction

Chromatography nowadays is widely used, with numerous applications in a wide range of application areas. Liquid and gas chromatography (LC and GC, respectively) are often said to be mature techniques. Indeed, reliable methods and instruments are available and the techniques can be applied by trained analysts, as well as by skilled experts. However, the word "mature" by no means implies that there are no more developments in the area. For example, in LC new column concepts (e.g. monolithic columns [1] and chips [2]) are developing strongly and instrumentation is progressing towards higher pressures [3] and two-dimensional analyses [4,5]. In GC, comprehensive two-dimensional separations form the most striking example.

For the practical user of chromatography it is increasingly difficult to judge the merits of new developments for his or her application. New techniques and methods are generally illustrated in the literature by one or a few specific applications. For example, in his pioneering paper on GC×GC, Phillips showed the benefits of the technique only for petrochemical products [6,7]. Almost all work in the first six years of GC×GC was restricted to this application area. A commonly voiced misconception during this time was that GC×GC was only applicable to petrochemical products. It was not until 1997, after Phillips had published the separation of polychlorinated biphenyls (PCBs) [8], that the technique slowly started to be adopted in other application areas.

Another example is the introduction of narrow-bore GC for fast separations. Initially, the method was used incorrectly, which significantly delayed its acceptance [9]. Although narrow-bore capillary columns are an excellent means for speeding-up GC separations, they are not suitable for all

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applications. For a while, fast GC in general and narrow-bore columns in particular suffered from a bad reputation. The eventual acceptance of fast-GC was aided by a series of review articles [9–11], describing the various options for faster separations and strategies for selecting the optimal approach.

As stated before, it is not always easy for chromatographers in practice to judge the benefits of new developments for their applications. When developing new instruments and techniques, it is also impossible to establish the advantages and limitations for each single application of chromatography. Fortunately, in practice this will hardly be necessary. We believe that by looking at commonalities between applications, the almost infinite number of applications can be reduced to a small number of generic application types. In this contribution, we will describe a novel scheme for classifying chromatographic applications. All chemical analyses (viz. qualitative and quantitative analysis) of chromatography are divided in three categories. For each of these application types, the general merits (and limitations) of new developments can easily be identified. This allows a rapid assessment of the value of new developments for each specific application of chromatography. We do not consider applications other than chemical analysis, such as measurements of physical properties by, for example, size-exclusion chromatography.

Two recent technological advances in chromatography, comprehensive two-dimensional gas chromatography (GC×GC) as such, and GC×GC in combination with multivariate analysis (MVA), will be used to demonstrate the proposed strategy. The advantage of these developments for the various types of applications will be described. Before we can do so, the relevant aspects of these new technologies must be briefly described.

1.1. Comprehensive two-dimensional gas chromatography

The concept of GC×GC was pioneered and advocated by the late J.B. Phillips [6,7]. A typical GC×GC system consists of two chromatographic columns in series. These columns separate components according to two different properties. Between the first- and second-dimension columns, a modulator is located. Small portions of the effluent from the first-dimension column are continuously trapped and released by this device. The result of a comprehensive two-dimensional separation can be visualized as a two-dimensional chromatogram, extending into three dimensions (two retention-time axes and an intensity axis). This technique provides an unsurpassed peak capacity and as a result, very detailed chromatograms.

1.2. Multivariate analysis

Multivariate-analysis techniques (MVA) are chemometrical tools for retrieving information from very large datasets, which are too complex for human interpretation. MVA techniques aim to reduce the data complexity. They result in strongly simplified representations of the data. In general, MVA techniques can be divided into two categories:

1. *Projection techniques* for the visualization of differences or similarities between the samples. The best-known example is principal-component analysis (PCA [12]). Since in many cases objects are described by (many) highly correlated variables, the dimensionality of the dataset is reduced if these variables can be replaced by a small number of principal components. Each sample in the data set is then described by a number of principal-component loadings (profiles in which the original variables are expressed) and principal-components scores (weight factors for each loading). The resulting projection provides a much clearer picture of the dataset and allows the selection of relevant variables. When differences between classes of samples are desired, discriminant-analysis techniques, such as principal-component-discriminant analysis (PCDA [13]) can be used.
2. *Calibration techniques* to establish relationships between measurements and, for example, product behaviour. Regression and calibration techniques aim to correlate the data set with one or more external variables. For example, in an industrial process the water content of a product can be a very important specification. By continuous monitoring of the process by near-infrared spectroscopy (NIR), a set of spectra is collected. By applying a multivariate-calibration technique, the water content in newly measured samples can be predicted, based on a previously constructed calibration model. Well-known examples of these techniques are principal component regression (PCR) and partial least squares (PLS) [14].

2. Theory

As stated in the introduction, we believe that all chromatographic applications can be classified into a small number of generic application types. The approach we propose here starts from the way in which the chromatographic signal is converted into the desired information on the sample. In our philosophy, only three translation strategies are applied. This implies that we distinguish only three generic types of applications in chromatography.

2.1. Type I: target-compound analysis

The most-common type of application is based on converting retention times into peak identities and the corresponding peak areas into amounts or concentrations. The actual information desired, are the concentrations of a finite number of pre-specified components. This strategy is generally referred to as “target-compound analysis”. The important keywords for this generic type of application are the following.

- *Isolation (local resolution)*

The compounds of interest ("targets") must be sufficiently separated from each other and from the sample matrix. Separation of other compounds present in the matrix is not required. The apparent resolution of target compounds may also be enhanced by using specific detectors.

- *Identification*

Obviously, unambiguous identification is very important in this type of application. Retention times (or Kovats indices) are useful in this respect. However, only specific detectors (particularly mass spectrometry) can provide irrefutable proof on compound identity.

- *Reliable calibration*

After recording the chromatographic signal, the peak areas must be transformed into concentrations. This can be achieved by calculating calibration factors from pure standards or reference materials. This requires the compounds to be stable and available in pure form. If this is not the case, FID response factors can be estimated using the theory of Scanlon and Willis [15].

- *Sensitivity*

In order to analyze low levels of compounds, a sensitive chromatographic system is required. This can be achieved by using sensitive detectors, suitable methods of sample preparation, and/or large-volume injection.

2.2. Type II: group-type analysis

In the second type of application, component groups are of interest, rather than individual components. This is, for example, the case when there is a strong correlation between the levels of specific component classes and the relevant product properties or if a particular group of components is toxic. Instead of "component groups", the name "pseudo-components" is also used. Pseudo-components often have structural properties in common, such as specific end groups, an identical number of aromatic rings, a specific configuration of double bonds, etc. Separation of the samples into individual component groups (or separating component groups from the matrix) provides valuable information. This strategy can be referred to as "group-type analysis". The main requirements for this type of application are the following.

- Group-type selectivity

Separation between the different component groups or between the component group(s) and the matrix is required. Separation within the groups is generally not necessary or even undesirable.

- Quantitative detection

Because the goal of this type of application is to obtain quantitative results on groups of components, a quantitative detector is required, which offers an equal response for all members of a component group. Whereas mass spectrometry may be an excellent tool for structure elucidation, it often fails in providing quantitative results on groups of components, due to large differences in ionization efficiencies between components in a group and other reasons.

- *Group identification*

Unlike in Type I (target-compound) applications, where only a limited number of individual peaks in the chromatogram are relevant, component groups have to be identified and quantified. Therefore, this type of application requires group-wise integration and quantification methods.

2.3. Type III: fingerprinting

In Types I and II applications, prior knowledge on the sample is required, i.e. the components or component groups of interest are known a priori. This is not always the case. A typical example is a product – that for unknown reasons – does not meet its specifications (in other words, it is "off-spec"). Such products may contain unknown components, which are responsible for the failure. In these situations, there will then be an urge to identify the responsible component(s) or component groups. One approach may be to quantify all components present in the sample and to correlate the results with the product properties. In most cases, this approach will be very demanding, if not impossible. A different approach is to consider the entire chromatogram as a "fingerprint" of the sample. By correlating this "fingerprint" with the product properties, component(s) or profiles can be traced to the "off-spec" condition. This approach heavily relies on MVA techniques.

The requirements for Type III ("fingerprinting") applications are the following.

- *Peak capacity*

Since each component present in the sample is potentially relevant, systems with a very high peak capacity are required to separate as many components as possible.

- *Retention-time stability*

Since MVA techniques generally require large sets of data and since recording chromatograms requires a considerable amount of time, ensuring system stability is a formidable challenge. Even minor shifts in retention times may render an entire dataset useless.

- *Detector stability*

Analogous to retention-time stability, detector response should be very stable overtime. Otherwise, erroneous conclusions may be drawn.

- *Dynamic range*

Since both major and minor components can be relevant, a wide dynamic range is required.

- *Multivariate-analysis techniques*

In order to correlate fingerprints with certain product properties, multivariate-correlation techniques are required.

Table 1
Overview of requirements for the three application types

Type	Application Type I: target-compound analysis	Application Type II: group-type analysis	Application Type III: fingerprinting
Requirements	Target compounds isolated ("local resolution")	Group selectivity	High peak capacity
		Separation between groups	High retention time stability
	Unambiguous identification	Quantitative detection	Reproducible response
	Reliable calibration	Group identification	Broad dynamic range
	High sensitivity	Group quantitation	Multivariate-analysis tools

Examples are partial-least squares (PLS) and principal-components regression (PCR).

The result of a "fingerprinting" application may be a set of peaks or a group of peaks that correlates with a certain product property, it may be a (multivariate) classification of samples, a library of chromatograms, etc. Identification of the identified (pseudo-)components will turn a "fingerprinting" application into a target-compound (Type I) or group-type (Type II) application.

Table 1 gives an overview of the three types of applications distinguished, summarizing also the main requirements for each.

3. Results

Chromatographic separations are performed to obtain information on specific samples. In the theory section, three ways of translating the chromatogram into the desired information have been discussed, which resulted in three types of applications. New developments in chromatography generally result in more or better information from faster, simpler, or cheaper methods. The consequences of such developments for each type of application can be very different. This can, for example, be illustrated by discussing the introduction of a new column with a different selectivity in GC. In case of a target-compound analysis in a very complex sample, the column will probably be of little use. On the old column, certain target components probably co-eluted (mutually or with matrix components), whereas other co-elutions are likely to occur on the new column. Multi-dimensional operation of the old and the new column may result in improved target-compound analysis, but only at the expense of increased efforts and analysis-time. For group-type separations (Type II), however, the new column could be very interesting.

Below, the application-type concept will be used to discuss the merits of two recent developments in chromatography, viz. GC×GC and its combination with MVA.

3.1. Target-compound analysis (Type I)

Since many target-compound analyses focus on very complex materials, there is a perpetual effort to develop separation systems capable of separating target components from one another and from the matrix. In many cases, the resulting chromatographic methods are related to product specifications, process control, environmental issues, legislation, etc. According to the requirements mentioned in the theory section of this paper, new developments that are useful for this type of application should provide adequate local resolution (peak capacity), unambiguous identification, and adequate sensitivity.

With respect to the isolation of target compounds in the chromatogram, GC×GC is superior to conventional one-dimensional GC. This may substantially aid the separation of target components from each other and from surrounding matrix peaks. With respect to unambiguous identification, GC×GC offers two retention coordinates instead of one. This improves the accuracy of peak assignment. However, there is still is no accepted two-dimensional alternative to the one-dimensional Kovats retention index. Moreover, coupling to MS requires very fast MS instruments (e.g. time of flight). Also, GC×GC–MS yields massive amounts of data. This makes the analysis and interpretation of GC×GC–MS data much more difficult than in the case of GC–MS. Finally, peak-compression provides an increase in sensitivity, typically by a factor of 4 or 5 in comparison with conventional one-dimensional GC [16].

The application of MVA techniques has already proven advantageous for Type I applications of GC×GC. Fraga et al. have reported the use of the generalized-rank-annihilation method (GRAM) for lowering the detection limits and resolving overlapping peaks [17]. Enhanced productivity may be a second advantage of the application of multivariate-analysis methods. van Mispelaar et al. reported the use of so-called multi-way methods for the rapid quantification of large datasets [18].

To illustrate the merits of GC×GC for Type I applications, the analysis of key flavour ingredients in a vanilla extract is used as an example. This application requires a truly high-resolution GC system. Fig. 1a shows the chromatogram of a vanilla sample. The indicated key components appear more-or-less separated from the matrix. A comprehensive two-dimensional chromatogram of the same vanilla sample, however, gives a better impression of the true complexity Fig. 1b. The sample is clearly much more complex than suggested by conventional one-dimensional GC. Components in Fig. 1b, which are in the same vertical line as the indicated, targeted compounds, would co-elute in the corresponding one-dimensional chromatogram. In this example, conven-

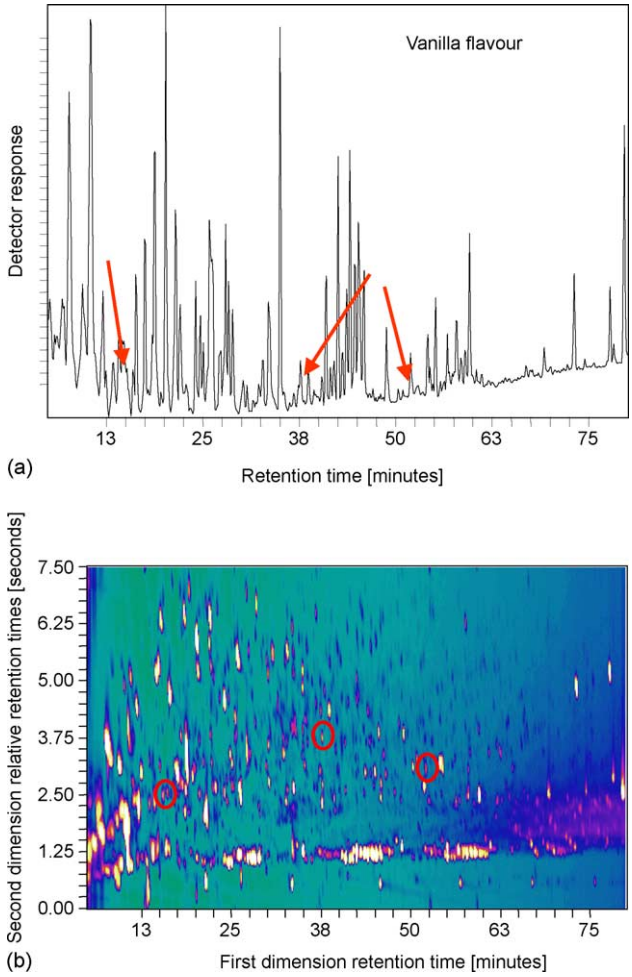

Fig. 1. (a) Separation of vanilla extract using one-dimensional GC. Key compounds are indicated by arrows. (b) Two-dimensional separation of vanilla extract. Circled compounds are of interest.

tional one-dimensional GC would clearly overestimate the concentration of the key vanilla components. It is for this reason that target-compound analyses in general (and within the flavour and perfume fields in particular) are often performed using GC–MS [19]. GC×GC–MS combines many of the advantages of GC×GC and GC–MS for Type I applications. Arguably, it is the best separation technique currently available [20]. Other examples in the literature of "target-compound analysis" by GC×GC include biomarkers in oil [21], key flavour compounds in essential oils [22,23], doping control [24], garlic-flavour analysis [25], and pesticides in food extracts [26].

GC×GC is extremely useful for Type I applications. However, it is not always the preferred method. For relatively simple samples (e.g. homologous series), the components can be separated in one dimension. For instance, Fraga et al. [17] reported the separation of a seven-compound mixture (branched benzenes) using GC×GC. Although it is a nice demonstration of the applicability of chemometric methods for quantification purposes, the separation of such compounds could probably also be achieved on a one-dimensional separation system.

3.2. Group-type analysis (Type II)

Many complex chemical and natural materials contain huge numbers of individual components. In general, the latter belong to only a limited number of chemical classes. A group of components belonging to one class is often referred to as a pseudo-component. For pseudo-component analysis, it is common practice in chromatography to first separate samples into as many components as possible, followed by grouping of the components belonging to each class. The final results are usually the concentrations of one or more components groups, rather than the concentrations of individual components. Pseudo-components can be related to sample properties, such as hydrogen conversion in hydrocarbon mixtures, toxicity in PCB containing samples, the degree of unsaturation of fatty acids, etc.

The first Type II applications of GC×GC have been reported in the field of petrochemical analysis [27]. Although these products virtually always contain an overwhelming number of components, the number of chemical classes is much-more limited. Structured separations are obtained by GC×GC, which substantially aids component identification [28]. In terms of the sample-dimensionality theory of Giddings [29], the dimensionality of the sample closely matches the system dimensionality, which equals two.

By far the main benefit of GC×GC for Type II applications is the possibility to obtain structured chromatograms. By matching the separation dimensions with the sample dimensions, component groups actually elute in bands parallel to the first-dimension axis.

In the theory section, three requirements were addressed for Type II applications: selectivity, quantitative detection and group-wise integration.

With respect to selectivity, GC×GC provides supreme possibilities. Since the first- and second-dimension generally involve columns coated with different stationary phases, components are separated according to two different (sets of) properties. An important possibility is the decoupling of volatility and polarity contributions to analyte retention [28]. Due to peak compression in the modulator GC×GC has a minor advantage over conventional one-dimensional GC with respect to quantitative detection.

The requirement for group-wise integration can – in principle – easily be met in GC×GC. The result of an ordered separation may be that components are grouped in classes. Therefore, group-wise integration can be achieved by drawing boxes around component groups. A summation within such a group yields a "group-area". Chemometric methods may help to assign chromatographic peaks to component groups or with the deconvolution of (partly) overlapping component groups. However, no publications have addressed these possibilities so far.

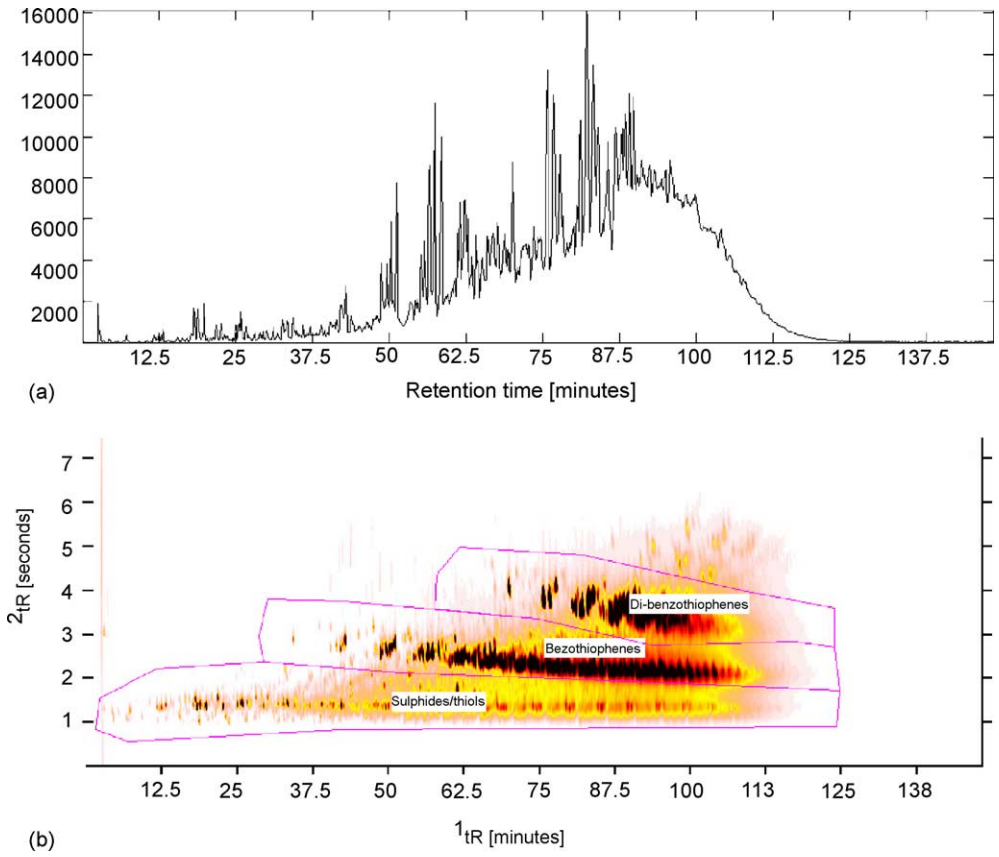

Fig. 2. (a) One-dimensional separation of cycle oil mixture with GC–SCD. (b) Group-type separation of cycle-oil mixture with GC×GC–SCD.

In order to illustrate the advantages of GC×GC for Type II applications, the group-type analysis of petrochemical products is used as an example. Traditionally, the group-type analysis of light hydrocarbon fractions is achieved using multi-dimensional column-switching GC. GC×GC has proven a successful alternative for the group-type analysis of such products. Fig. 2a shows the one-dimensional chromatogram of a cycle-oil mixture obtained with sulphur-chemiluminescence detection (SCD). Although present capillary GC columns achieve impressive separation power, they are not really adequate for such complex samples. The combination of columns coated with different stationary phases in heart-cutting multi-dimensional GC, is of rather limited value for group-type separations [30]. The combination of a boiling-point separation in the first dimension and a polarity separation in the second dimension results in a highly ordered chromatogram, in which the various pseudo-components can easily be distinguished. Fig. 2b shows the comprehensive two-dimensional separation of a cycle-oil mixture with GC×GC–SCD. The boxes indicate the regions in which specific compound groups elute and they are also used for quantitative purposes.

Other applications of Type II analysis by GC×GC are the determination of the degree of unsaturation of fatty acids [31,32] and the classification of PCBs according to planarity [33].

3.3. Fingerprinting (Type III)

One specific research area that thrives on the "fingerprinting" approach is the identification of "biomarkers" (or "disease markers") in systems biology. In this application area, the correlation between sick and healthy patients and their metabolomic-profiles needs to be established. This is achieved by analysing samples from sufficiently large numbers of "test subjects" (human, animal, or vegetable) of known condition (either suffering from a particular disease or syndrome, or not). Correlations between the chromatographic profiles and the status of the objects can be established using pattern-recognition tools. This allows the identification of biomarkers for a particular disease, which can then be used to detect diseases at an early stage or to assess the effectiveness of drug treatments. The field of proteomics relies heavily on this approach [34].

In the theory section, the requirements for Type III applications have been identified as peak capacity, retention-time stability and dynamic-range.

With respect to peak capacity, GC×GC provides roughly the product of the peak capacities of the first- and second-dimension columns. This is a much higher number than what can be obtained in conventional, one-dimensional chromatography. GC×GC, hence, clearly facilitates the recording of detailed fingerprints of complex materials.

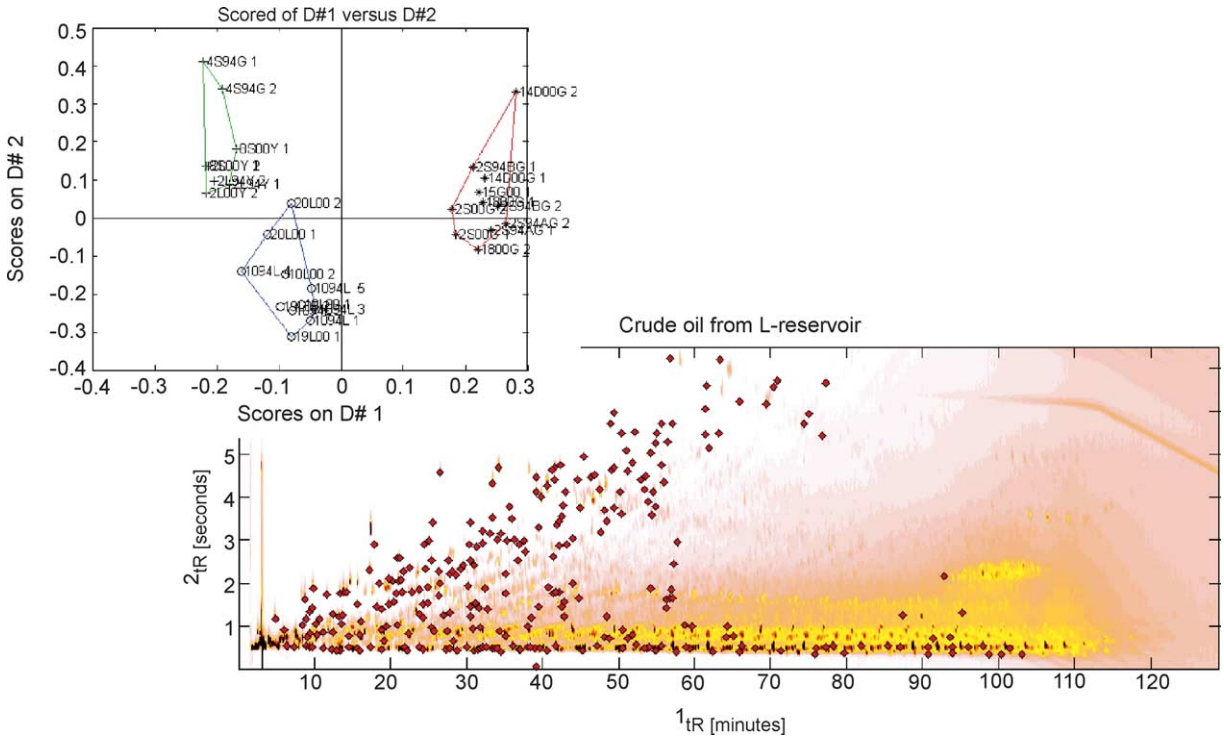

Fig. 3. Clustering of crude-oil samples according to their origin.

For the second requirement, retention-time stability, the problems are aggravated in GC×GC in comparison with conventional one-dimensional GC. In GC×GC separations, retention-time shifts can occur in both dimensions. This makes data pre-processing a formidable challenge for GC×GC. Fortunately, developments in both GC instruments and column technology have resulted in much-more-stable instruments.

With respect to the dynamic range, GC×GC suffers from the application of narrow-bore columns in the second dimension. Narrow-bore, thin film columns have a low sample capacity and can compromise the wide dynamic range of the applied detectors, such as flame ionization detectors and mass spectrometers.

The use of MVA techniques is often needed for this type of application. Since even conventional one-dimensional GC is able to generate hundreds of peaks, conventional interpretation does not allow a fast correlation between sample composition and product properties. In many cases, a combination of components can be correlated with product performance, patient status, etc. Univariate methods are not able to deduce highly correlated component profiles. Multivariate-analysis methods can, however, be used, since they are highly suitable for reducing the complexity of the samples. In two-dimensional electrophoresis, this approach has, for example, been used to classify two-dimensional maps of lymphomas [35].

For successful multivariate analysis, data-preprocessing techniques (such as scaling, aligning, and variable selection) are obligatory to overcome, for example, retention-shifts.

Fingerprinting applications using MVA of conventional one-dimensional GC have hardly been described. Publications in this field concern the prediction of mineral-oil properties based on gas-chromatographic separations [36], the detection of the origin of fuel spills [37], and metabolic profiling of genomics with GC–MS [38].

For the combination of GC×GC with MVA techniques, hardly any references can be found [39,40]. However, the combination of GC×GC and MVA is potentially very powerful, since the fingerprints obtained from GC×GC

Table 2
MVA requirements and application examples of GC×GC in combination with MVA for the three generic application types

Type	Application Type I: target-compound analysis	Application Type II: group-type analysis	Application Type III: fingerprinting
Multivariate analysis (MVA)	Component assignment Component alignment Quantification	Group assignment Group alignment Group quantification	Preprocessing (alignment, scaling) Multivariate techniques
Application example	PCB's Key flavour components	*cis*/*trans* classification Hydrocarbon group type analysis	Metabolomics (biomarkers) Crude-oil clustering

Table 3
Summary of the advantages and disadvantages of GC×GC and GC×GC–MVA in comparison with conventional one-dimensional GC

	Application requirements	(Dis)advantages of GC×GC	Additional (dis)advantages of MVA
Type I: target-compound analysis	High peak capacity	Much higher peak capacity	Possible deconvolution of overlapping peaks
	Reliable component identification	Two retention axes	Possible correction for retention time shifts[a]
	Reliable quantification	Greater reliability due to less peak overlap	Possibility of deconvolution
	Adequate Sensitivity	Peak compression	Signal/noise filtering
Type II: group-type analysis	Selectivity	Structured chromatograms; decoupling of analyte parameters (e.g. volatility and polarity)	Group-deconvolution
	Constant detector response within group	N/A	N/A
	Group-quantification	Structured separations; less peak overlap	Potentially very much faster quantitation
Type III: fingerprinting	Peak capacity	Much higher peak capacity	Data-reduction and clustering techniques
	Retention-time stability	Retention shifts may occur in two dimensions	Possible correction for retention time shifts[a]
	Reproducible response	N/A	Possibility for scaling[a]
	Dynamic range	Reduced by use of narrow-bore columns in two dimensions	Signal/noise filtering

[a] During data-preprocessing stage.

contain very much information. To fully exploit this potential, powerful data-preprocessing techniques are needed. Below, we will illustrate the power of MVA methods using an example from oil production.

Differentiation between highly similar crude-oil reservoirs (i.e. wells within one oil field) is very difficult, but vital for monitoring the oil production. GC×GC provides very detailed chromatograms with up to 6000 components. The challenges for chromatography and MVA of such samples and data are formidable. Every chromatogram represents a very large datasets. This means that many samples are typically required to describe such data. Moreover, the comparison of samples is hindered by retention-shifts and by imperfections in the integration. Variable-selection techniques have been used to reduce the dataset to approximately 300 components. Although it is quite feasible to separate 300 peaks in one-dimensional GC, the 300 peaks from GC×GC are pre-selected for relevance and absence of interference from irrelevant peaks.

The selected components were subjected to a discriminant analysis, resulting in the clustering of the samples into three reservoirs (Y, L and G) [41].

Fig. 3 shows the GC×GC chromatogram of a crude oil indicating the peaks that are used to build a discrimination model.

Table 2 summarizes the requirements for each application type and lists examples of published applications.

Table 3 reviews the advantages and disadvantages of GC×GC – as a stand-alone application or in combination with MVA techniques – in comparison with conventional one-dimensional GC.

4. Discussion and conclusion

All applications of chromatography can be classified into three generic types of applications: target-compound analyses, group-type separation and fingerprinting. The implications of new technological developments can be rigorously assessed at the generic level. The general benefits and limitations for each application type can be translated into practical advantages and disadvantages for the numerous specific applications of chromatography. The classification scheme should aid the developers of new technologies to understand and explain the potential of their products to the chromatographic community. It should also aid practical chromatographers in understanding the implications of new developments for their specific applications.

The proposed approach has been used to assess the merits of GC×GC, and the additional advantages of its combination with MVA. For each of the three generic types of applications, clear benefits and limitations could be identified and recommendations for specific applications could be deduced.

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