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GC×GC-MS HYPHENATED TECHNIQUES FOR THE ANALYSIS OF VOLATILE ORGANIC COMPOUNDS IN AIR

Cecilia Arsene,[1] Davide Vione,[2,3] Nelu Grinberg,[4] and Romeo Iulian Olariu[1,*]

[1] Faculty of Chemistry, Laboratory of Analytical Chemistry, "Al. I. Cuza" University of Iasi, Carol I 11, 700506 Iasi, Romania

[2] Dipartimento di Chimica Analitica, Università di Torino, Via Pietro Giuria 5, 10125 Torino, Italy

[3] Centro Interdipartimentale NatRisk, Università di Torino, Via L. da Vinci 44, 10095 Grugliasco (TO), Italy

[4] Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Rd., Ridgefield, CT 06877-0368

[*] Corresponding author: *oromeo@uaic.ro*

Comprehensive two-dimensional gas chromatography (GC × GC) and its direct applications to measurement of volatile and semivolatile organic compounds in air are reviewed and discussed. The paper includes a brief discussion of the instrumental set-up and theory for the comprehensive GC × GC hyphenated with different detection techniques. Several reviewed types of modulators demonstrate that the applications of comprehensive GC × GC are still under development, underlying the flexibility of the system as well. The fundamental differences between one-dimensional and two-dimensional gas chromatography, regarding their potential to provide both qualitative and quantitative information, are also presented. The present article focuses on reported applications dealing with the analysis of volatile and semivolatile organic compounds from air (gas and particles related), but some data related to other sample types analyzed with comprehensive GC × GC are also briefly presented. The paper supports the idea that there is a good reason for interest in comprehensive GC × GC, which seems to be a suitable technique for applications in the separation of complex mixtures of volatile and semivolatile compounds.

Keywords: comprehensive GC × GC, volatile/semivolatile organic compounds, air, gas, particles

Introduction

Numerous chemicals are distributed worldwide in the most important environmental compartments including atmosphere, hydrosphere and lithosphere and many of these compounds can be hazardous both to ecosystems and to humans.[1] Currently, the atmospheric chemistry research is focused on the reactive trace gases and particles relevant to climate change. Reactive trace gases relevant to air quality and to the atmosphere include molecules of both organic and inorganic origin. Most of these chemicals result either as a mixture of direct emissions from sources such as fossil fuel combustion, vegetation and biomass burning, or as species formed by *in situ* processes.[2] Current research is focused on measurements of the variability of such chemicals over timescales ranging from seconds for reactive chemistry to years for long-term anthropogenic impacts. However, the progress in atmospheric chemistry analytical tools demonstrates that new classes of compounds are important and new detectors are needed for their measurement. An example is the recently realized need to quantify semivolatile organic compounds (SVOCs), which can be found in either the gas or particle phase. SVOCs are either directly emitted or produced in the atmosphere upon oxidation of volatile organic compounds (VOCs).[3,4]

It is well known that a typical atmospheric chemistry field project is mainly aimed at simultaneously measuring a large amount of organic and inorganic species in the gas, semi-volatile, and particle phases. However, the complex atmospheric matrix represents a challenge for all research groups that are constantly developing faster, smaller, more sensitive and selective analytical tools. They consist of spectroscopic, mass spectrometric and chromatographic techniques for use on several sampling sites such as aircraft, balloons, ships, mobile vans or fixed ground points.[5]

Gas-phase species are measured by a wide suite of spectroscopic, chromatographic and mass spectrometric approaches, the choice of which is largely depending on the stability, reactivity and chemical structure of the investigated compounds. The need for sensitivity and selectivity is universal in analytical chemistry applications, and comprehensive two-dimensional gas chromatography (GC × GC) seems to provide high-performance separations in terms of selectivity, sensitivity, speed and structure determination.[6] Sensitivity requirements for atmospheric chemistry depend on the abundance and variation of the target species but are typically in the range of parts per billion (ppb) to parts per quadrillion (ppq) levels by volume. Instrumental approaches tend to either target specific molecules or provide bulk measurements of broad classes of compounds. Moreover, atmospheric analytical chemistry has four additional requirements: rapid time resolution, portability, ease of calibration and stability with respect to ambient temperature and pressure fluctuations. Therefore, new apparatus are needed to continue pushing bounds of sensitivity and time resolution for both compound-specific and bulk analysis of key species.[5]

Due to the specific vapor pressure, for the separation and analysis of a wide range of VOCs, biogenic VOCs or halogenated VOCs in both aqueous and gaseous samples, gas chromatography (GC) is undoubtedly the method of choice. Many publications related to the subject were always giving information related to the quality assurance (QA), quality control (QC) and statistical data analysis for such measurements.[7-10]

Actually, GC is identified as an important analytical technique suitable for applications in both qualitative and quantitative analysis. For the analysis of complex samples, where separation capability and selectivity are the driving forces of the required process, hyphenation of different technique is currently the preferred strategy. The role of hyphenation in instrumental analysis and the types of instrumental dimensions that can be effectively coupled were described by Hirschfeld in 1980.[11] Gas chromatography, mainly in tandem with mass spectrometry (MS), can be used in the analysis of a variety of real-life samples of environmental (sampling from aircraft,[12] atmospheric particles,[13-19] outdoor and indoor air,[20-24] water,[25] agriculture[26]), biological,[27-32] food and beverages,[33-37] drugs,[38] flavor and fragrances [39] and industrial concern.[40] Moreover, we should still keep in mind that although the instruments are highly sophisticated, a number of severe analytical problems have to be considered in the analysis of volatile organic constituents in the atmosphere. They are associated with pre-concentration on traps, interaction of analytes with surfaces (adsorption, blanks), water removal, trapping material and artifact production by O_3.[41,42]

Comprehensive two-dimensional gas chromatography (hereafter abbreviated as GC × GC) began to attract attention more than 15 years ago[43,44]. In GC × GC, two columns are connected sequentially, with a modulator positioned between them. Typically the first is a conventional column and the second is a fast-type one. Over the years, quite a number of reviews on GC × GC have been published on early[45-48] or more recent fundamental developments.[49-53] Ledford et al. in 2000 proposed the concept of comprehensive three-dimensional gas chromatography (GC^3), which was demonstrated by using modified GC × GC apparatus.[54] By revealing the immense complexity of an air sample analyzed by Prof. John P. Phillips, with a GC × GC chromatogram containing some 5000 peaks (most of them at the low parts per trillion -ppt- level), GC × GC was motivating the development of higher dimensional techniques, such as GC^3.

The publications of Adahchour et al. in 2006 and 2008 are excellent reviews and prove that the GC × GC hyphenated technique has become a rapidly emerging and increasingly successful instrumental tool, especially after 2003.[49,50] Comprehensive GC × GC is considered as an innovative, powerful separation tool, holding much promise for complex sample analysis. By 2000, novel comprehensive GC × GC instruments suitable for analyzing VOCs mixtures were developed.[55,56]

A comprehensive GC × GC instrument is based on a set-up ensuring that a total two dimensional separation is completed within the run time of the first-dimension analysis.

Improved resolution for all sample constituents and no loss of time are the major characteristics of GC × GC over multidimensional gas chromatography (MDGC, GC-GC),[47,57] whose capabilities are limited only to target analysis situations.[44] The interesting aspect of comprehensive GC × GC *vs.* GC-GC is that the whole sample is subjected to two independent separations, and that the two-dimensional separation is completed in the run time of the first separation.[48]

Nowadays, comprehensive GC × GC has become a powerful and widely applicable technique for the characterization and analysis of a variety of volatile and semi-volatile compounds in complex samples[48] from petroleum industry,[58-60] surfactants,[61] odor and fragrance products,[62-64] biological systems,[65] pyrolysis product stream,[66] food and beverages,[67,68] tobacco essential oils,[69] marine sediments[70] and atmospheric aerosols.[71,72] Marriott et al. in 2004 suggested that comprehensive GC × GC can also be used for probing selected molecular processes.[73]

It is believed that GC × GC offers tremendous potential for the further elucidation of thousands of GC sample types the researchers have to deal with. However, this technology is not one that is accessible to average gas chromatographers, and a successful GC × GC system or accessory will require both highly integrated hardware and software and comparable academic qualifications for the newcomer in the field.[47,74] An important advantage is that the technique is offering an unprecedented separation power for a huge number of different organic compounds in several systems, including the analysis of complex ambient air composition. However, the general thought is that this technique is demanding, requires a high amount of liquid nitrogen and manpower and, compared to GC-MS does not offer substantially higher compound speciation. Therefore, it is still rarely used in ambient VOC analysis in atmospheric chemistry, but recent instrumental developments could help resolving most of the cited problems.[75]

General principles governing the comprehensive GC × GC analysis

In comprehensive GC × GC analysis, two GC separations based on distinctly different separation mechanisms are used as shown in Figure 1. The interface between these two systems is called modulator and has as the main function of cutting and refocusing narrow adjacent fractions of the first column eluate and, after focusing, to release them rapidly into the second column.[49] Actually, the modulator is the heart of the technique as it moves repetitively at a period about one-fifth that of the peak widths on the first column.[76] The small fractions from the first dimension are refocused into narrow pulses of about 0.01 s width, and launched into the second-dimension column.[48] In comprehensive GC × GC analysis, the modulation period plays an important role as a long period risks under-sampling of the peaks, although faster sampling may exacerbate the wrap-around process (*vide*

infra).[77] Actually the purpose of the second column is to achieve an orthogonal separation as compared to the first column, with the main result in the form of separation along two axes, each with unique selectivity. Using the approach of calculation of thermodynamic indices for the set of target analytes, modeling of a comprehensive two-dimensional GC can be successful.[78]

Normally, in comprehensive GC × GC the second-dimension separation should be finished before the release of the next fraction[73] and, if not, the so called wrap-around situations occur.[49] A wrap-around situation is a phenomenon when the second-dimension peaks show up in later modulation than in which they were injected, which is caused by second retention times exceeding the modulation time.[49]

As a general rule, in most applications of comprehensive GC × GC, samples are firstly separated on a normal bore column ((15-30) m× (0.25-0.32) mm i.d. × (0.1-1) μm film tickness (d_f)) containing a non- or semi-polar stationary phase. After modulation, each individual fraction is injected onto a much shorter, narrower column. Typical dimensions are (0.5-2) m × 0.1 mm i.d. × 0.1 μm d_f, and the column contains a (medium)polar or shape-selective stationary phase.[48,49,51] The secondary column is a short, narrow-bore capillary, also operated at linear velocities well above optimum. Nevertheless, it can deliver 3000-5000 theoretical plates, which is sufficient for the purpose at hand. Hydrogen carrier gas is advantageous in comprehensive GC × GC, because it maintains column efficiency at higher linear velocities than helium does.[47]

A novel approach to comprehensive GC × GC separation, operating in a new region of the "GC × GC optimization pyramid" was proposed by Harynuk and Marriott in 2006.[79] The proposed technique relies on the use of short primary columns in order to decrease elution temperatures of analytes, which will in turn allow GC × GC to be applied to mixtures of less volatile compounds or to thermally labile ones. By using short primary columns, resolution and efficiency in the first dimension is lost. However, speed is gained and the second column in GC × GC may still provide additional resolution and analytical separation of compounds with different chemical properties.

Junge et al. in 2007 tested capillary column sets with shorter lengths and smaller inner diameter in both the first (^{1}D) and second (^{2}D) dimensions, for fast chiral and achiral separations.[80] The first column set used by the authors included a ^{1}D chiral column of 10 m × 0.1 mm i.d., with 0.1 μm d_f, and a ^{2}D BP20 column of dimensions 30 cm × 0.05 mm i.d., with 0.05 μm d_f. While conventional analysis of the investigated sample mix takes about 75 min, a fast experiment was conducted within a total analysis time of 23 min. Elution times on the ^{2}D column were less than 4 s, and adequate enantioselective separations of limonene, linalool, α-isomethyl ionone and citronellol were achieved. It was found that the latter component precluded a further increase in speed of the GC × GC separation with enantioselective phase, as reduced resolution could occur otherwise. For a fast achiral analysis, the column set

incorporated a BP20 column (5 m × 0.1 mm i.d. and 0.1 μm d_f) serially coupled to a BGB1701 column (0.3 m × 0.05 mm i.d., 0.05 μm d_f, effective length 15 cm). The system operated at a heating rate r_T = 35 °C min^{-1}. With this combination, a considerable reduction in analysis time could be obtained in comparison to the reference column set operated under conventional conditions. The complete separation of all the investigated compounds, including various isomers, was obtained with a total retention time window of ~4 min in the first and less than 1 s in the second dimension. Peak widths at half-height in the second dimension were about 25-50 ms. Overall, similar relative peak positions in the two dimensional space were obtained in both the normal and fast GC × GC results, suggesting that method translation from normal to fast conditions should be possible.[80]

Important requirements for an appropriate GC × GC analysis involve the following aspects: *(i)* the narrow fractions subjected to modulation should not be wider than about one-quarter (or σ) of the peak widths in the first dimension, typically 5-30 s, in order to maintain the integrity of the first-dimension separation. The second-dimension run times should be of the order of 2-8 s, with processes governed by an isothermal behavior;[81] *(ii)* it is required to use fast detectors, with data acquisition rates of, preferably, at least 100 Hz. This is a consequence of the extremely narrow second-dimension peaks, typically displaying 50-600 ms widths at the baseline. Such a goal is usually obtained with a comprehensive GC × GC coupled with time-of-flight mass spectrometry (TOF/MS).[48,82] Indeed, detectors with small internal volume, short rise time and high data acquisition rate are required to ensure proper reconstruction of the second-dimension chromatograms.[48] Moreover, it is known that when a TOF/MS detector is coupled to a GC × GC system, the additional dimension of mass-to-charge ratios is added to the data. Such highly-structured data are proving to be both incredibly valuable when coupled with novel chemometric techniques, and incredibly challenging to manage and manipulate. GC × GC-TOF/MS data cubes containing on the order of 110 million data points per hour for a single sample are not uncommon. Efficient means of sifting through these data to extract useful information is one of the current challenges facing the technique.[83]

An issue that is attracting increasing interest is the optimization of the column combinations. There are indications that, with (highly) polar compounds, a “reverse”, *i.e.* a polar × non-polar column combination will offer better performance than the conventional non-polar × polar set up.[48] However, in spite of more than 15 years of claims of the ability of GC × GC to resolve an overwhelmingly larger number of peaks than one dimensional GC, and in spite of the theoretically proven potential of GC × GC to have an order of magnitude larger peak capacity than one dimensional GC, the peak capacity of currently practiced GC × GC does not exceed the peak capacity attainable from one dimensional GC with the same analysis time and the same minimal detectable concentrations (MDC).[84]

In comprehensive GC × GC, orthogonality represents a relatively simple estimator, independent of the length of the second-dimension (^{2}D) column types, which can be tested for a wide range of applications. Orthogonality means that the two columns utilize different retention mechanisms. The target is to predict the maximum separation space for the two-dimensional separation,[77] with the amendment that the ^{2}D column operates essentially under isothermal conditions. By using the Kovats retention indices, it is possible to estimate vapor pressures and the enthalphic contribution to the activity coefficient. Furthermore, the retention factors (k) of the compounds and their elution temperatures are estimated and eventual chromatograms can be predicted.[85] Moreover, it is believed that in a general sense the goal of GC × GC is to obtain maximum column orthogonality and maximum use of separation space, in order to achieve the best resolution for the components.

In orthogonal GC × GC (elution times for each dimension are treated as statistically independent), a non-polar or low-polarity phase should be used for the first dimension. This happens because the separation mechanism on such a phase is, generally speaking, based on analyte volatility only. For the second dimension a variety of phases can be selected, depending on the desired analyte-stationary phase interactions.[49] Various studies have been undertaken to identify the best stationary phase for the second-dimension column, both under orthogonal and non-orthogonal approaches,[86,87] as well as column dimensions [88] and optimum flow conditions. By means of suitable choices it is possible to considerably improve separations in GC × GC (combination of a first-dimension column having a 0.25-0.32 mm internal diameter with a second one featuring an i.d. of 0.15-0.18 mm seems a good choice).[89] By employing a supplementary gas supply, one can also control the effects of pressure drop on absolute retention matching (*i.e.* the assignation of peak identities to specific peak positions).[90] It is also suggested that it may be better to use larger diameter columns in the second dimension, when analyzing samples in which the concentrations of the analytes or matrix components are unknown and may be high. Indeed, such a set-up will lessen the chances and consequences of overloading in the second dimension.[91]

An exponential relationship has been reported between the secondary column peak width and the amplitude enhancement. Amplitude enhancement means that peaks in GC × GC are often higher than in single-column GC, with increased sensitivity as a consequence. To maximize such an effect, significant effort should be made to produce thermal modulation units and column combinations that can deliver secondary column peak widths below 200 ms, ideally below 100 ms.[92] An enhancement in sensitivity for an individual isolated peak of about 4-5 may be achieved in orthogonal GC × GC compared to a one-dimensional separation, and it is possible to develop a simple model to account for that.

The non-orthogonal approach in comprehensive GC × GC (*i.e.* use of columns with somewhat similar retention mechanism) may have some advantages over the orthogonal GC × GC, providing improved chromatographic behavior and improved peak shape of some

complex analyte classes. Examples are aldehydes, ketones, alcohols and carboxylic acids analyzed by GC × GC with flame ionization detector (FID), [93] pyrazyne fractions interfered by thiophenes, ketones and pyridines as volatile fractions of coffee beans.[94] Moreover, an interesting application of comprehensive GC × GC is related to the analysis of the enantiomeric pairs of a system, by using enantioselective (cyclodextrin) phases (*e.g.* separation of enantiomeric pairs of monoterpene hydrocarbons and oxygenated monoterpenes).[95]

Modulators and detectors in comprehensive GC × GC

The GC × GC instrument itself shows much similarity to a conventional GC. In fact, most modern conventional gas chromatographs can be rather easily converted into a GC × GC instrument. Here, we will describe only some components that make the difference between the conventional GC and comprehensive GC × GC.

Modulators

The heart of any GC × GC system is the modulator, which is the interface between the two columns. It controls the flow of analytes from the first to the second column, acting as a gate that performs injections in a consistent and reproducible fashion. Many common commercial modulators are based on jets of cold gas applied to a segment of capillary between the two separation columns. This creates a cold spot where analytes are trapped through partitioning or freezing. The application of a heating pulse while turning off the cold jet remobilizes the trapped material and injects it as a narrow plug into the second column. Other modulation options include valves or pressure-based pneumatic devices, which are now being commercialized as well, or segments of metal columns that can be resistively-heated through the application of an electrical pulse.[83]

Ledford and Billesbach in 2000 demonstrated that by pulsing cold and hot jets of gas onto a modulator tube with solenoid valves, two-stages thermal modulation can be obtained without the complexity of moving parts in the vicinity of the capillary columns.[96] Existing modulators produce injection pulses of about 50 ms width (at half-height) under tightly controlled experimental conditions. Pulse width may exceed 100 ms under more typical conditions, which are actually unfavorable situations requiring longer than optimal modulation periods. Indeed, long modulation periods significantly reduce the peak capacity of the first dimension and, therefore, that of GC × GC systems as a whole.[84] In order to identify the appropriate operation conditions in comprehensive GC × GC, it was proposed the term modulation ratio (M_R) which actually describes the sampling rate.[97] The authors define this term as the ratio of 4 times the first column peak standard deviation (4σ) divided by the modulation period (P_M), or 1.6985 times the half-height width of the peak (w_h). It is suggested

that for the analysis of trace compounds, requiring precise measurements, the experiments should be conducted with M_R of at least 3. For semiquantitative methods or the analysis of major components, an M_R of about 1.5 should suffice.

Cryogenic modulation

Comprehensive GC × GC separations can be accomplished in many ways, and the most common methods used today involve various forms of thermal modulation between the first and the second column.[47] Modulators of the cryogenic-jet type use liquid carbon dioxide or nitrogen for cooling. They are robust and user-friendly.[48,98] Attractive features of these systems are increased reliability of identification, due to the enhanced resolution, and improved detection limits. Moreover, by using a cryogenic modulation system a true baseline can be established, for instance in the determination of atmospheric organics.[99] It is suggested that a GC × GC combined with a longitudinally modulated cryogenic system (LMCS) may be a powerful separation tool to improve data quality when environmental samples containing many impurities are analyzed.[76] With LMCS, it is necessary to mechanically modulate the trap between two column connectors to transport output from the first to the second column.

Marriott et al. in 2000 compared the thermal sweeper and the cryogenic modulator in an interlaboratory study, using a complex sample containing many semi-volatile compounds. They found that the two methods behaved in an analogous manner toward the delivery of GC × GC results, with key peak parameters of width and symmetry showing good correlation.[100] Kristenson et al. in 2003 investigated, evaluated and compared different cryogenic and one heated GC × GC modulator(s) for the analysis of high-boiling halogenated compounds.[101] The cryogenic modulators investigated were: *(i)* the longitudinally modulated cryogenic system; *(ii)* the liquid-nitrogen-cooled jet modulator (KT2001); *(iii)* a dual-jet CO_2 modulator; *(iv)* a semi-rotating cryogenic modulator and *(v)* a CO_2 loop modulator (KT2003). The heated modulator was the slotted heater system (sweeper). The latter uses a thick-film column to trap the analytes, which are then released by heating. Each modulator was optimized, with respect to analyte peak widths at half height in the second dimension. In the mentioned work n-alkanes, chlorinated alkanes, polychlorinated biphenyls (PCBs) and fluorinated polycyclic aromatic hydrocarbons (F-PAHs) were used as test analytes. The investigations performed by Kristenson's group revealed that: *(i)* The flow rate of the cooling agent was found to be an important parameter, *i.e.* the flow rate of the coolant in the KT2001, and of the liquid CO_2 in the other cryogenic modulators; *(ii)* For the slotted heater, stroke velocity and pause time were important parameters. This modulator had a limited application range in terms of temperature, due to the need of having a 100 ^{o}C difference between sweeper and oven temperature; *(iii)* All cryogenic modulators were found to be suitable for the GC × GC

analysis of high-boiling compounds, but the CO_2 modulators are to be preferred to the KT2001 due to a wider application range and slightly narrower peaks.

In a study performed by Junge et al. (2007) it was shown that comprehensive GC × GC with cryogenic modulation has potential for fast chiral separations, including enantiomer separations of limonene, linalool, citronellol and α-isomethylionone.[80]

In 2008, Tobias et al. reported for the first time on the coupling of comprehensive GC × GC to online combustion - isotope ratio mass spectrometry (C-IRMS), the system being equipped with a LMCS unit.[102] A problem that is still found in comprehensive GC × GC is related with the undesirable overlapping and smearing of peak bands between adjacent heart-cut sections. However, there are thoughts that use of a second thermal modulator may solve the problem.[47]

Flow modulation

In 2006, Kochman et al. presented a new approach of flow-modulation, comprehensive two-dimensional gas chromatography-mass spectrometry (GC × GC-MS) with supersonic molecular beam (SMB) and a quadrupole mass analyzer.[103] Flow modulation uniquely enables GC × GC-MS to be achieved even with the limited scan speed of quadrupole MS (qMS), and its 20 ml min^{-1} column flow rate is handled, splitlessly, by the SMB interface. Flow-modulation GC × GC-SMB-MS is thought to share all the major benefits of a GC × GC system and combines them with those of a GC-MS, featuring: *(i)* increased GC separation capability; *(ii)* improved sensitivity via narrower GC peaks; *(iii)* improved sensitivity through reduced matrix interference and chemical noise; *(iv)* polarity and functional group information via the order of elution from the second polar column. In addition, GC × GC-SMB-MS is uniquely characterized by the features of GC-MS with SMB, with enhanced and trustworthy molecular ion plus isotope abundance analysis (IAA), for improved sample identification and fast fly-through ion source response time. The flow-modulation GC × GC-SMB-MS was explored by the authors with complex matrices such as diesel fuel and pesticides in agricultural products.[103] It was also found that the main benefit of GC × GC-MS over GC-MS is the reduction of matrix interference, which results into increased sensitivity in the analysis of samples in complex matrices.

Pulsed flow modulation

In 2008, Poliak et al. combined a pulsed flow modulation (PFM) from comprehensive GC × GC with a quadrupole-based mass spectrometric system (MS).[104] The coupling was done via a supersonic molecular beam (SMB) interface using a triple-quadrupole system as the base platform, which enabled tandem mass spectrometry (MS-MS) to be carried out. In PFM, sample compounds that elute from the first GC column are temporarily stored for a few seconds in a fused silica transfer line. Then they are pulsed periodically injected by ~ 25 ml

min^{-1} He gas pulse into the second column. Simultaneously, the first column flow is temporarily stopped. After the pulse, 20 ml min^{-1} He develops the chromatography in the second column for a few seconds. PFM is a simple GC × GC modulator that does not consume cryogenic gases, while providing tunable second GC × GC column injection time. Therefore, it enables the use of quadrupole-based mass spectrometry regardless of its limited scanning speed. Similarly to flow modulation, the 20 ml min^{-1} flow rate in the second column is handled, splitlessly, by the SMB interface without affecting the sensitivity. The combinations of PFM GC × GC-MS with SMB and PFM GC × GC-MS-MS with SMB were explored by the authors with the analysis of diazinon and permethrin in coriander. PFM GC × GC-MS with SMB is characterized by enhanced molecular ion and tailing-free fast ion source response time. The system enables universal pesticide analysis with full scan, and data analysis with reconstructed single ion monitoring on the enhanced molecular ion and another prominent high-mass fragment ion. The elimination of the third fragment ion used in standard three ions method, results in significantly reduced matrix interference. GC × GC-MS with SMB improves the GC separation, and thereby the identification ability by using libraries. GC-MS-MS with SMB provides better reduction of matrix interference compared to GC × GC-MS. However, the authors also conclude that GC × GC-MS-MS does not seem to further reduce matrix interference compared to GC-MS-MS. Moreover, unlike GC × GC-MS, GC × GC-MS-MS is incompatible with library identification, but it is beneficial to have both GC × GC and MS-MS capabilities in the same system.[104]

Differential flow modulation

In 2000, Seeley et al. developed a GC × GC instrument with a six-port diaphragm valve fitted with a sample loop, to couple the primary and secondary column.[55] The technique was called differential flow modulation GC × GC. It provides high speed, high resolution and high sensitivity. Although the differential flow modulation was passing only 90% of the effluent exiting the primary column to the secondary column, the authors were classifying their technique as a comprehensive one. In fact, the primary column effluent was sampled throughout a chromatographic run at a frequency (1 Hz) high enough to retain the chromatographic separation produced by the primary column. The technique was successfully used to analyze mixtures of alkanes, alkenes, aldehydes, alcohols, aromatics, esters and ketones, with high speed and high resolution. However, the theory of optimization of GC × GC systems suggests that, under optimal conditions, injection of a sample into the second-dimension column should take no longer than a few milliseconds.[105]

Microfluidic Deans switch

Seeley et al. in 2007 proposed a new model of modulator, microfluidic Deans switch, which can be used in comprehensive GC × GC.[106] The Deans switch is actually a low duty cycle

modulator which samples only a small portion of the primary column effluent. Its properties (simplicity and wide temperature range) make the Deans switch a promising alternative to existing modulation techniques. However, the Deans switch produces inconsistent transfer of components from the primary to the secondary column if the primary peaks are under-sampled. The Deans switch GC × GC was validated by analyzing the aromatic content of gasoline by a fast analysis (<10 min) or a slower analysis (33 min run time). The authors found that in the slower analysis, quantitative results and relative standard deviations (RSDs) were in excellent agreement with the differential-flow GC × GC and GC-MS results. It is thought that the Deans switch can be an effective modulator, if modulation ratios greater than about 2.5 are employed. An important issue is the thermal mass of the device, which should be reduced as much as possible to allow uniform heating and avoid cold spots that could reduce the chromatographic performance for higher boiling compounds.

Other modulators used in real measurements

In comprehensive GC × GC the modulator is continuously sampling small fractions of the compound stream eluting from the first-dimension column, and introduces them into the second-dimension column. As a result of the modulation, a single compound is divided into several peaks. Under these circumstances, the total peak area of the modulated compound is the sum of the individual peaks. Kallio and Hyotylainen in 2008 have demonstrated that GC area calibration is suitable for quantitative GC × GC. It can be used instead of GC × GC area calibration, as long as one meets prerequisites of quality (separation of the target analytes from each other by GC and separation from matrix by GC × GC) and quantity (concentrations to be determined above the limit of quantification (LOQ) of GC, where LOQ is defined as ten times the standard deviation of the noise).[107] The peak areas produced by GC × GC are equal to those obtained in one-dimensional GC, because the mass transfer from the first-dimension to the second-dimension column in comprehensive GC × GC is normally quantitative. However, the modulator is the key bottleneck limiting the performance of existing GC × GC configurations. When comparing the performance of GC × GC to one dimensional GC and in order to achieve the full potential of GC × GC, duration of the injection from the modulator into the second-dimension column should be reduced as much as possible.[84]

A new mode of operation for comprehensive two-dimensional gas chromatography (GC × GC), stop-flow GC × GC, was introduced recently.[108] In this technique, the flow in the primary column is stopped for a brief period of time during each modulation cycle, allowing for a secondary separation time that is longer than would otherwise be permitted by the modulation period in conventional GC × GC. This allows the modulation period and the secondary separation time to become independent variables, and greatly increases the flexibility of the system. Actually, stop flow GC × GC can provide higher resolution than conventional GC × GC in the first dimension, especially for early-eluting peaks. It maintains a

comparable secondary separation in a similar amount of time and is significantly reducing the analysis time required for a GC × GC run.

Detectors

Due to the narrow nature of GC × GC peaks, the detector must be capable of acquiring data with a high rate. Common detectors that are used include the flame ionization detector (FID), electron capture detector (ECD) and time-of-flight mass spectrometer (TOF/MS). Other detectors that can be used include both the nitrogen and sulphur chemiluminescence detectors (NCD and SCD), as well as the nitrogen-phosphorous detector.[83] For sulphur- and phosphorus-containing compounds, flame photometric detection can be successfully used[109]. Newer high-speed quadrupole mass spectrometers (qMS) can also be used in a limited fashion.[110,111]

The performance of three commercially available electron-capture detectors (ECDs) was compared in a work performed by Kristenson et al. in 2003. The authors were looking for the optimal conditions to obtain narrow peak widths in GC × GC, *i.e.* to avoid band broadening caused by the cell volume.[101] The most important parameters were the flow rate of the make-up gas and the detector temperature, which both should be as high as possible. Comparison of analyte peak widths obtained with ECD mode and FID showed that ECDs exhibited band broadening compared to the FID. However, under the used conditions the narrowest peaks were obtained with a micro-ECD, which had a cell volume of only 150 μL.[101] Comprehensive GC-GC with ECD was also used by Korytar et al. (2004, 2005), who optimized methods for the separation of polychlorinated biphenyls, diphenyl ethers, naphtalenes, dibenzothiophenes, dibenzo-p-dioxins and polychlorinated dibenzo-p-dioxins, dibenzofurans, terphenyls, toxaphene, organohalogenated pesticides, polybrominated and polychlorinated biphenyls.[86,87]

Although a majority of the GC × GC work is being carried out using non-selective detection (*i.e.* FID), greater analytical selectivity can be achieved by combining the high resolving power of GC × GC with mass spectrometry or chemiluminescence. The modern bench-top, single-quadruple GC-MS system is a very sensitive instrument, capable of acquiring data in synchronous single ion monitoring (SIM) mode and of detecting target analytes down to levels at, or below, parts per billion (ppb). Hybrid GC techniques have been used for over a decade to elucidate complex mixtures of organic compounds in the environment. Recent advances in GC × GC-TOF/MS allow detailed classification and quantification of compounds previously unresolved with traditional GC-MS.[66,110,112,113]

GC × GC coupled to a rapid-scanning quadrupole mass spectrometer (GC × GC-qMS), with scan speed of up to 10,000 amu s^{-1} is a powerful separation and identification technique for the analysis of many complex samples.[114] The Perkin-Elmer Clarus 500 rapid-scanning qMS, operated in electron ionization (EI) or electron-capture negative ion (ECNI) mode was

found to be an excellent detector for GC × GC.[115] At an acquisition rate of 20 Hz, it enables detection of peaks with a baseline width of at least 300 ms. Such a system is thus suitable for many, and certainly for most organohalogen applications. However, although LODs of the femtogram order can be reached, it is suggested that further work will be needed before the GC × GC-ECNI-qMS technique is recommended as a replacement for GC-HRMS in dioxin analysis.

Mass spectrometry with soft ionization techniques (*i.e.* ionization without fragmentation of the analyte molecules) for gaseous samples exhibits interesting analytical features for direct applications (*i.e.* direct inlet mass spectrometric on-line monitoring) as well as MS detection method for GC. Chemical ionization (CI), field ionization (FI) or photo-ionization (PI) methods are interesting alternatives for the ionization source.[116] In 2008 it was documented for the first time that three widely encountered problems (limited precision in MS quantification, the matrix in which the standard is dissolved, determination of the relative response factor representative for a group of analytes with similar functionalities, and electron impact fragmentation patterns) affect precise and accurate quantification of VOCs by thermal desorption-gas chromatography-mass spectrometry (TD-GC-MS), and strategies to deal with these problems were proposed.[117]

Wang et al. in 2005 reported the two-dimensional representation of gas chromatography-soft (field) ionization mass spectrometry as a retention time versus molecular mass diagram.[40] The authors used a GC separation by a chromatographic column with a polar stationary phase. Because the GC separation is partly following the specific polarity-based interactions in the column, and the soft ionization mimics a non-polar separation, the two-dimensional representation resembles a comprehensive two-dimensional gas chromatographic diagram (GC × GC). However, the GC separation step usually implies a temperature increase during the chromatographic run (*i.e.* the GC oven temperature program) and, therefore, also exhibits a considerable fraction of “volatility-type separation” characteristics. For this reason, the orthogonality of GC with a specific column (*e.g.* polar phase) and soft-ionization MS is somewhat restricted.

Zimmermann et al. in 2008 proposed that by transforming the retention time axis in a manner that the alkane row forms a horizontal line for the case of gas chromatography with single photon ionization (SPI) time-of-flight mass spectrometer (GC–SPI-TOF/MS), one obtains a representation of the two-dimensional comprehensive separation with increased orthogonality. The compound-class separation characteristics was also very similar to the one obtained in normal GC × GC comprehensive two-dimensional gas chromatography plots.[116] In analogy to the acronym “GC × GC” for comprehensive two-dimensional gas chromatography, the application of gas chromatography with soft ionization mass spectrometry for comprehensive multidimensional separation of complex samples is named “GC × MS”.[118,119] In addition to the GC × MS approach with SPI, Mitschke et al. in 2006

applied resonance enhanced multi-photon ionization (REMPI) with TOF/MS, at different ionization wavelengths in order to obtain highly selective, sensitive and soft ionization of predominantly aromatic compounds.[118]

Analyte quantification and detectability

Comprehensive two-dimensional gas chromatography (GC × GC) has the potential to provide both qualitative and quantitative analysis. Comprehensive GC × GC may achieve significant simplification and cost savings if an inexpensive, universal detection method such as flame ionization detection (FID) is used at least for routine analyses. However, in such instruments calibration by the traditional methods becomes a larger problem and the characterization of complex mixtures using GC × GC-TOF/MS may represent a possible solution. The alternative is to transfer/translate the method to less expensive instrumentation using a less complex detector.[78]

Normally a GC × GC result comprises a two-dimensional plot with axes that represent total first dimension (^{1}D) and second dimension (^{2}D) time, respectively. There are few major differences between GC and GC × GC systems, mainly related to both the way the data are obtained and the software used to interpret those data. GC × GC data appear at the detector as a train of short second-dimension chromatograms. The data system then cuts the data into individual second-dimension chromatograms and aligns them into a signal matrix. Typically these chromatograms are viewed as contour plots with the X-axis representing retention on the primary column and the Y-axis representing retention on the secondary column.[83] As shown by Welthagen et al. in 2003, a bubble plot seems to be suitable for a rapid visual recognition of pattern changes in monitoring studies.[120]

In comprehensive GC × GC, quantitative analysis is performed on the basis of a relationship established using peak area, volume or height. Peak area is rarely used, since peak envelope is affected by the phase of the modulation.[121] Despite this problem, nowadays there is commercial software for quantitative GC × GC analysis, for example HyperChrom from Thermo Scientific, GC Image from Zoex and 4DGC × GC-TOF/MS from Leco.[107] In additional to the traditional integration methods, the nature of GC × GC data enables the use of chemometric techniques. [51,122,123] It was demonstrated that the GC × GC/tri-PLS (tri-PLS – trilinear partial least squares) methodology holds considerable promise. In principle, GC × GC/tri-PLS can be readily automated, saving considerable time over other methodologies such as ASTM D1840, which is an off-line spectroscopic method for the analysis of naphthalene content in jet fuel. [122]

Methods for comparing datasets produced by comprehensive GC × GC were proposed considering the most challenging aspects shown by GC × GC data: inconsistency and complexity. A technique proposed by Hollingsworth et al. in 2006 registers (or aligns) GC ×

GC datasets to remove retention-time variations; normalizes intensities to remove sample amount variations; computes differences in local regions to remove slight mis-registrations and differences in peak shapes; employs color (hue), intensity and saturation to simultaneously visualize differences and values; and uses tools for masking, three-dimensional visualization, and tabular presentations to significantly improve comparative analysis of GC × GC datasets.[124]

In order to fully achieve the separation power of comprehensive GC × GC, a means of predicting and optimizing separations based on operational variables was developed. The proposed approach initially calculates the enthalphy (ΔH) and enthropy (ΔS) for the target compounds from the experimental input data. The approach used to calculate thermodynamic retention indices (ΔH and ΔS), termed computer-assisted stationary phase design (CASPD), was described by Dorman et al. in 2002. Its goal is to predict the chromatographic separation and stationary-phase selectivity.[125] For extension into comprehensive GC × GC, it was proposed that CASPD2d simulates GC × GC separations as a function of the many variables involved. Sufficient input data are obtained rapidly using GC × GC – TOF/MS instrumentation, then CASPD2d optimizes variables for both GC × GC–TOF/MS and GC × GC-FID, including peak identification for the latter.[78] The authors suggest that by using the estimated thermodynamic retention indices, all column and runtime variables including stationary phase composition can be simultaneously optimized, by comparing the performance of a large number of separations. In a work performed by Vogt et al. in 2007 by using direct thermal desorption (DTD) coupled with GC × GC–TOF/MS, an automated compound classification for ambient aerosol samples was presented.[126] The authors pointed out that the classifiers, based on fragmentation patterns, retention time and mass spectral transformations were incorporated into software scripts for automated classification. Recently, a new method for the calculation of the percentage of separation space used was developed using Delaunay's triangulation algorithms (convex hull).[127] The method was successfully applied to the selection of the most convenient column set and the geometrical parameters of the second column, for the analysis of 49 target compounds in wastewater.

In a brief background review to quantification in comprehensive GC × GC, Amador-Munoz and Marriott suggest an interesting comparison between GC and GC × GC. One-dimensional gas chromatography produces a single measured peak in the chromatogram, with a single retention time and a single peak response (either area or height). In contrast, comprehensive GC × GC is producing a series of modulated peaks at the detector. Therefore, the peak metrics of retention, area and height for one component will not represent simple single values for one peak, but rather values which are derived from the multiple peak distribution generated by the modulation process.[123] The authors also take under discussion the modulation ratio (M_R) concept, which was proposed and intended to clarify the meaning of modulation number (n(M)) in GC × GC, which was a rather poorly defined parameter.

Based on prior studies that introduced the M_R concept, the role of quantitative analysis has been investigated through calculation of the peak areas and peak area ratios of selected series of modulated peaks in GC × GC. It has been shown that adequate quantitative analysis and calibration can be accomplished by using selected major modulated peaks for each compound, a procedure which may simplify quantitative interpretation of GC × GC data.

The effect of the amount of matrix compounds in comprehensive GC × GC separation of polycyclic aromatic hydrocarbons (PAHs) was investigated by Kallio and Hyotylainen in 2007.[128] In their study, the second dimension column was overloaded by progressively increasing the matrix amount. The separation was evaluated by inspecting peak widths, asymmetries, resolution, retention times, peak areas and volumes of the target compounds. For quantitative analysis, the authors tested two different calibration methods for both raw sediment extracts and cleaned extracts, *i.e.* for extracts in which the matrix was removed by a liquid chromatographic clean-up step. The authors found that the quality of the separation was not significantly disturbed in terms of peak width, asymmetry and resolution when the amount of matrix was increased. However, the depth of the valley between PAH and preceding matrix peak increased with an increase in matrix amount, and the repeatability of retention times, peak areas and volumes decreased. Moreover, the authors observed that in quantitative analysis, calibration by using areas had a tendency to underestimate the trace amounts of PAH, especially for the non-cleaned samples. In the case of volume calibration, the most accurate results were obtained by external calibration for both cleaned and non-cleaned samples.

Short overview on volatile/semi-volatile organic compounds measurements performed by comprehensive GC × GC

Gas chromatography is still the technique of choice for analyzing both volatile and semi-volatile compounds. In the past few years, comprehensive two-dimensional gas chromatography has attracted considerable attention in organic trace-level analysis.[110] The analysis of chemicals with very small concentrations has always been a challenge. Method development in trace analysis tends to focus on the enrichment of the chemical of interest through trapping on a solid adsorbent. If concentrations are very low, the volume of the sample (air or aqueous) can be increased in order to increase the final concentration of the analyte. Whilst specific detectors can be used to increase the detection limit, the main disadvantage is that often the sample size is quite small and hence increasing the volume is problematic. Micro extraction by packed sorbents (MEPS) may solve the problem by reducing the need for increased volume size of the sample to be analyzed, and by its possibility to be used with any chromatographic technique.[110]

In 2008, in a review on recent developments in the application of comprehensive two-dimensional gas chromatography, Adahchour et al. have discussed a number of papers on GC × GC of micro-contaminants in environmental samples related to air and aerosols.[51] Table 1 presents some data relevant to real measurements of both volatile and semi-volatile organic compounds, performed in various matrices (aerosols, air) by comprehensive GC × GC. The Table includes the general chemical classes investigated by different research groups, as well as technical data related to the system used for the measurements.

In 2001, Truong et al.[76] compared the performance of a comprehensive two-dimensional GC × GC (equipped with either LMCS or thermal sweeper modulators) for semi-volatile aromatic analysis. The results obtained were similar to those reported by Marriott et al. [100]

Seeley et al. have demonstrated that a dual secondary column configuration (GC × 2GC) greatly facilitates compound identification. In this case the flow that exits the modulator (*e.g.* a Microfluidic Deans Switch) is split into two parts, each delivered to a different column with its own detector at the end. GC × 2GC increases the separation efficiency of mixtures containing organic compounds with electronegative functional groups (*e.g.* alcohols, aldehydes, ketones, esters).[56] To demonstrate the performance of the GC × 2GC system, the authors combined several mixtures to produce a 55-component sample containing the following compounds: C_5-C_{13} n-alkanes, C_1-C_8 alcohols, C_3-C_8 2-alcohols, C_4-C_7 2-methyl-2-alcohols, C_3-C_8 and C_{10} acetates, C_3-C_{11} aldehydes, C_3-C_8 2-ketones, and C_6-C_{10} alkyl aromatics. The configuration proposed by the authors seems well suited for analyzing samples that contain oxidized or halogenated compounds, but not as useful for samples dominated by hydrocarbons.

Volatile organic compounds play a key role in the processes that generate urban photochemical smog and tropospheric ozone. Determining the dominant reactive species is, therefore, highly important. In an early study, Lewis et al. used GC × GC to characterize complex samples from urban air. They have isolated more than 500 chemical species of volatile organic compounds, including over 100 multi-substituted monoaromatics and volatile oxygenated hydrocarbons.[99] The mono-aromatic complexity in gasoline, gasoline vapors and urban air was studied by Hamilton and Lewis, who compared comprehensive GC × GC–FID and fast GC–TOF/MS.[138] The authors also emphasized the ability of each technique to speciate at high isomeric complexity. Analysis of urban air by comprehensive GC × GC indicated the presence of 147 mono-aromatic species with up to 8 carbon substituents on the ring, while 130 such compounds were found in gasoline. Comparison of the highly detailed 2D GC × GC chromatograms for air and gasoline vapors proved that these were remarkably similar in some aromatic regions, with almost identical distributions of C_3 and C_4 alkyl-substituted aromatic compounds. In contrast, the proportion of higher substituted aromatics in air diminished significantly relative to fuel vapor. It is suggested that the above-mentioned

observation demonstrates visually the impact of evaporative emission sources in urban environments.

In a project on *in situ* measurements of atmospheric VOCs, a thermal desorption (TD) unit coupled with GC × GC–FID showed the presence of several hundreds well-separated peaks in air samples taken at a ground station in Crete.[129] In order to facilitate peak identification, cartridge samples were collected and subjected to GC × GC–TOF/MS analysis. The identified compounds included cyclic and acyclic alkanes, PAHs, oxygenated aromatics, alcohols, aldehydes and ketones. In a subsequent paper the authors used the same instrumental set-up to measure C_7–C_{11} aromatics and n-alkanes in order to investigate photochemical reactions.[130]

Comprehensive GC × GC was presented by Shimmo et al. as a novel approach for the analysis of aerosol particles.[13] Partially oxidized organic compounds, associated with up to 2.5 μm diameter ($PM_{2.5}$) aerosols collected in London, United Kingdom, have been analyzed using direct thermal desorption coupled to comprehensive gas chromatography-time of flight mass spectrometry (GC × GC-TOF/MS).[131] Extremely complex chromatograms were obtained within this study, with over 10,000 organic components isolated from around 10 μg of aerosol material in a single procedure and with no sample pre-treatment. Chemical functionalities observed ranged from alkanes to poly-oxygenated species. Because of the complexity, ordered structures were not immediately visible and the added selectivity of TOF/MS was urgently required. Oxygenated VOCs (o-VOCs) found in the London aerosol were actually inventoried on the basis of ordered structures visualized by selecting suitable m/z ions: 52 linear, 21 mono-aromatic and 64 cyclic o-VOCs were identified. At least 100 o-VOCs with longer chain lengths and increasing substitutions were observed, for which insufficient information could be retrieved from the MS library.

In 2005, Ryan et al. conducted a study aimed at investigating the influence of orthogonality in comprehensive two-dimensional gas chromatography.[77] Their experiments were designed to fulfill the following requirements: test sample containing substances distributed over the whole range of properties relevant to the method (a range of chemical classes, covering an adequate range of analyte polarities, including alkanes, alcohols, terpenes, monoaromatics, naphthalene), suitable carrier gas flow rate, and suitable temperature at which the components enter the column. In fact, these are the only parameters that influence the second-dimension separation.

Kallio et al. in 2006 also used GC×GC–TOF/MS to identify organic compounds in atmospheric aerosols collected in Finland, as part of the QUEST campaign.[133] Several organic compounds were identified, some of them apparently for the first time. Altogether, about 50 compounds were identified on the basis of mass spectra and linear retention indices. The identified compounds included oxidized monoterpenes, acyclic alkanes, alkenes, ketones and aldehydes, as well as a few alcohols, acids and aromatic compounds. It was found that manual search was more accurate with the investigated samples. Although the authors also

used a GC × GC-FID, the conclusion of the study was that structure-related information could not be directly obtained from this system. However, the GC × GC-FID chromatogram indicated that the sample components were nicely spaced along the second axis. As is shown by Welthagen et al., developed search criteria and rules could be used to group peaks into distinct chemical classes. This strategy has been applied to the GC × GC chromatograms of $PM_{2.5}$ aerosol collected in Augsburg (Germany), using TOF/MS fragmentation patterns and GC × GC retention times.[120] Such an approach was actually needed to facilitate interpretation of the more than 15,000 compounds detected in a typical $PM_{2.5}$ sample.

A comprehensive GC × GC-FID was used for the in-situ measurement of VOCs at Hohenpeissenberg, southern Germany.[139] In that campaign, the authors used a GC × GC set-up similar to that reported by Xu et al.[131] They performed a comparison to routinely made GC-MS measurements and observed good agreement for a variety of anthropogenic and biogenic ambient VOCs, ranging in concentration from below the detection limit (0.1 pmol mol^{-1}) to 180 pmol mol^{-1}.

Ochiai et al. in 2007 performed a study on the characterization of nanoparticles (29–58 nm in diameter) in roadside atmosphere, by using high resolution time-of-flight mass spectrometry (HR-TOF/MS) plus simultaneous detection with a nitrogen phosphorus detector (NPD) and a quadrupole mass spectrometer (qMS).[140] For all systems the column set was the same, BPX-5 × BPX-50. Exact mass measurement served to increase selectivity and group-type separation of, *e.g.*, oxygenated polycyclic aromatic hydrocarbons (oxy-PAHs). In addition, 50 compounds were identified in the nanoparticle fraction on the basis of exact mass measurements and NIST library information. TD–GC × GC–NPD/qMS showed the presence of 15 N-containing compounds. Seven of these were tentatively identified by TD–GC × GC–HR-TOF/MS, the other eight were not identified because the reverse factor for the NIST library search (>800) and/or the mass errors (<± 6mDa) were outside the acceptance criteria selected by the authors. The reverse factor is the normalized dot product with square-root scaling of the submitted multi-spectrum and the library multi-spectrum. TD–GC × GC–qMS, with a limited scan range of m/z 177–280 to achieve a data acquisition speed of 27 Hz, provided proper conditions for the quantification of selected PAHs at ultra-trace levels (pg [μg-PM]$^{-1}$).

Within this short history on VOCs measurements by comprehensive GC × GC, there is an important number of works related to method development that should also be mentioned.[78,84,116,136] Welthagen and coauthors have successfully coupled comprehensive two-dimensional GC × GC with soft single photon ionization (SPI) TOF-MS, providing a three-dimensional separation technique.[136] They used two selective columns for the GC × GC approach (carbowax and 50% phenyl-50% methyl-polysiloxane) in order to separate according to “polarity” and “polarizability”. The soft ionization mass separation step was again used to mimic a “volatility-type separation”. The outcome was a three-dimensional

comprehensive separation space. This comprehensive three-dimensional separation approach opens up new possibilities in the future of ultra-complex sample separation.[116] In order to compare the general performance of GC × GC and of one-dimensional GC under controlled conditions, Blumberg et al. in 2008 have used a test mixture of 131 known semi-volatiles for which nearly all components could be identified both by GC × GC and by 1D-GC. Peak capacities of both analyses could be experimentally evaluated, and it was possible to predict the general separation performance of the method in the analysis of more complex mixtures.[84]

Recently, data from the determination of organic compounds in particles from wood pyrolysis, with particle sizes of 30–100 nm were reported.[137] Particles were analyzed by four techniques: comprehensive GC × GC-TOF/MS, GC-TOF/MS, GC-qMS and aerosol mass spectrometry (AMS). In the case of chromatographic techniques, particles were collected on a filter and analyzed off-line after sample preparation. In the case of AMS, particle analysis was performed directly from the particle source. Target compounds in the samples were polyaromatic hydrocarbons and n-alkanes. From the obtained data the authors concluded that the GC × GC-TOF/MS provided the best separation efficiency and the most reliable identification and quantification of compounds.

Conclusions

Comprehensive two-dimensional gas chromatography (GC × GC) reveals that in chemical terms the world is much more complex than one-dimensional separation techniques show. Indeed, almost any analyzed matrix consists of many more chemical species than previously detected. Based on a large number of publications, it can be concluded that the separation power of comprehensive GC × GC has considerably improved during the last decade. Comprehensive GC × GC is a technique that is ideally applied to the separation of complex mixtures of volatile and semivolatile compounds from various matrices. The technique offers better sensitivity and permits better peak identification. It is suitable for sample screening because it gives a considerable amount of information about the investigated sample. The main advantages of comprehensive GC × GC include a vastly expanded separation space, ability to resolve hundreds or thousands of peaks and improved sensitivity. From a practical point of view, comprehensive GC × GC is compatible with all types of injection systems and sample handling techniques used in one-dimensional GC, because the first column is a conventional one. GC × GC reduces the need of complex sample preparation procedures and tends to eliminate the interference problems that are critical in conventional GC separations. Comprehensive GC × GC hyphenated with different detection techniques (TOF/MS, qMS, FID) is a powerful analytical tool that finds use in various fields of research. They include environmental science, petrochemicals, food and beverages, pharmaceuticals, flavors,

fragrances and forensics. Because of its high degree of separation, which can provide unambiguous characterization, comprehensive GC × GC hyphenated with MS detectors has the potential to penetrate into new application areas.

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Table 1: Applications of comprehensive GC × GC in real measurements of volatile and semivolatile organic compounds in atmospheric samples (air and aerosols). Selected publications related to method development and modeling are also presented.

Matrix type	Components	Instrument	Special amendments (modulation)	First dimension column	Second dimension column	Other conditions
Method development[56]	C_5-C_{13} n-alkanes C_1-C_8 alcohols C_3-C_8 2-alcohols C_4-C_7 (2-methyl-2-alcohols) C_3-C_8; C_{10} acetates C_3-C_{11} aldehydes C_3-C_8 2- ketones C_6-C_{10} alkyl aromatics	Gas chromatograph Perkin-Elmer Autosystem XL (Norwalk, CT, USA) with electronic pneumatics and dual flame-ionization detectors FIDs.	A high speed 6-port diaphragm valve (DV22-2116, Valco, Houston, TX, USA).	**DB-624** capillary column 15 m × 0.250 mm i.d. 1.4 μm d_f (6% cyanopropylphenyl + 94% dimethyl polysiloxane)	**DB-Wax** column 5 m × 0.25 mm i.d. 0.25 μm d_f (polyethylene glycol) **DB-210** column 5 m × 0.25 mm i.d. 0.50 μm d_f (trifluoropropylmethyl polysiloxane)	The oven temperature program: 40 ^oC (for 0.4 min) ramp to 60 ^oC at 40 ^oC min^{-1}, ramp at 120 ^oC at 30 ^oC min^{-1}, ramp to 200 ^oC at 22.5 ^oC min^{-1} (for 1.0 min). The carrier gas was H_2. Primary column flow 0.75 ml min^{-1}. Secondary column flow 20 mL min^{-1}.
Air, gas[129]	Acyclic alkanes Cyclic alkanes Acyclic alkenes Cyclic alkenes Aromatic hydrocarbons Oxygenate aromatics Alcohols Aldehydes Ketones Esters Nitriles	Gas chromatograph GC6890 (Agilent, Wilmington, DE, USA) equipped with FID detector.	Jet modulated GC× GC cooled and heated (Zoex, Lincoln, NE. USA).	**DB-5** capillary column 30 m × 0.25 mm i.d. 1 μm d_f (5%-phenylmethylpolysiloxane)	**Carbowax column** 1 m × 0.1 mm i.d. 0.1 μm d_f (polyethylene glycol)	The oven temperature program: first column 50 ^oC to 200 ^oC at a rate of 2.5 ^oC min^{-1}; the second column from 30 ^oC to 180 ^oC at a rate of 2.5 ^oC min^{-1}. The modulation period was 6 s. The carrier gas was He.

	Halogenated HCs					
Air, gas[130]	n-Alkane C_7-C_{11} aromatic hydrocarbons	Gas chromatograph GC6890 (Agilent, Wilmington, DE, USA) equipped with FID detector.	Jet modulated GC× GC cooled and heated (Zoex, Lincoln, NE. USA).	**DB-5** capillary column 30 m × 0.25 mm i.d. 1 μm d_f (5%-phenylmethylpolysiloxane)	**Carbowax** column 1 m × 0.1 mm i.d. 0.1 μm d_f (polyethylene glycol)	The oven temperature program: first column 50 ^oC to 200 ^oC at a rate of 2.5 ^oC min^{-1}; the second column from 30 ^oC to 180 ^oC at a rate of 2.5 ^oC min^{-1}. The modulation period was 6 s. The carrier gas was He.
Air, aerosols[131]	Linear o-VOC Substituted mono aromatic o-VOC Cyclic o-VOC	Gas Chromatograph Agilent 6890N and a Pegasus III reflectron TOF/MS.	Liquid nitrogen cryo-jet Pegasus 4D (Leco, St. Joseph, MI, USA).	**HP-5** capillary column 10 m × 0.18 mm i.d. 0.18 μm d_f (5% phenyl+ 95% methyl-polysiloxane).	**DB17** column 1.66 m × 0.10 mm 0.10 μm d_f (14% cyanopropylphenyl-polisiloxane).	The oven temperature program: 40 ^oC (for 5 min) ramp at 3.5 ^oC min^{-1} to 270 ^oC (for 10 min). The carrier gas was He. Primary column flow 1 mL min^{-1}.
Method development[77]	Alkanes Alcohols Terpenes Monoaromatic Naphthalene	Gas chromatograph Agilent 6890 (Agilent Technologies, Burwood, Australia).	Longitudinally modulated cryogenic system (LMCS) (Chromatography Concepts, Doncaster, Australia).	**BPX5** capillary column 20 m × 0.25 mm i.d. 0.25 μm d_f (low polarity: 5% phenyl methyl polysilphenylene siloxane phase) **BP20** capillary column 20 m × 0.25 mm i.d. 0.25 μm d_f	**BPX5** column 0.8 m × 0.1 mm i.d. 0.1 μm d_f (low polarity: 5% phenyl methyl polysilphenylene siloxane phase) **BP20** column 0.8 m × 0.1 mm i.d. 0.1 μm d_f	The oven temperature program: 50 ^oC to 240 ^oC at 5 ^oC min^{-1} held at 240 ^oC for 3 min. Modulation period for the LMCS 3.5 or 8 s. The carrier gas was H_2. Primary column flow 1 mL min^{-1}.

				(polar: polyethylene glycol phase)	(polar: polyethylene glycol phase)	
Air, aerosols[132]	n-alkanes n-alkanals n-alkan-2-ones PAHs Oxygenate-PAHs Terpenes Terpenoids	Gas chromatograph Agilent 6890 (Agilent Tehnologies, Palo Alto, CA USA).	Thermal modulation system.	**ZB-5 -** capillary column 20 m × 0.25 mm i.d. 0.25 μm d_f (non-polar phase)	**BGB-1701** column 0.7 m × 0.1 mm i.d. 0.1 μm d_f (semi-polar phase)	The oven temperature program: 60^{o}C (for 5 min), ramp at 25^{o}C min^{-1} to 300^{o}C held at 300^{o}C for 5 min. The carrier gas was He.

Air, aerosols[133]	n-hexane Toluene Diesel-range hydrocarbons PAHs.	Gas chromatograph HP6890 equipped with an HP7683 automatic injector and a FID (Agilent Technologies, Palo Alto, CA, USA).	Semi-rotating cryogenic modulator.	**HP-5MS** capillary column 20 m × 0.25 mm i.d. 0.25 μm d_f (5% phenyl methyl polysilphenylene siloxane phase).	**Carbowax** column 0.5 m × 0.05 mm i.d. 0.1 μm d_f (polyethylene glycol)	The oven c program: 60 ^{o}C (for 4 min), ramp at 5 ^{o}C min^{-1} to 240/300 ^{o}C held at 240/300 ^{o}C, 15 min. The carrier gas was H_2/He. The modulation period was 3 s.
					DB-17 column 0.5 m × 0.05 mm i.d. 0.1 μm d_f (50% phenyl+ 50% dimethyl polysiloxane)	
					BGB-1701 column 0.7 m × 0.1 mm i.d. 0.1 μm d_f (14% cyano+ 86% dimethyl polysiloxane).	The oven temperature program: 60 ^{o}C (for 5 min) then ramp at 5 ^{o}C min^{-1} to 300 ^{o}C held at 300 ^{o}C 8 min. The carrier gas was H_2/He. The modulation period was 3 s.
		Gas Chromatograph Agilent 6890 and a Pegasus II TOF/MS (LECO, St. Joseph, MI, USA)	Laboratory made cryogenic dual-jet modulator.	**HP-5MS** capillary column 20 m × 0.25 mm i.d. 0.25 μm d_f (5% phenyl methyl polysilphenylene siloxane phase)	**BGB-1701** column 0.7 m × 0.1 mm i.d. 0.1 μm d_f (14% cyano-86% dimethyl polysiloxane)	The carrier gas was He. The interface temperature was 300^{o}C and for ionization source was 250^{o}C. Ionization was done EI. The modulation period was 5 s.
Methods development[134]	PAHs	Gas chromatograph Agilent 6890N coupled	Modulator Zoex Modulator loop type	**BPX-5** capillary column 30 m × 0.25 mm i.d.	**BPX-50** column 1 m × 0.1 mm i.d.	The oven temperature program: 50 ^{o}C (for 3 min),

		with Micromass GTC-TOF MS and with thermal desorption system GERSTEL TDS-2.	KT2004, (Zoex corporation, Huston, TX, USA).	0.25 μm d_f	0.1 μm d_f	ramp at 5 ^{o}C min^{-1} to 350 ^{o}C. The modulation period was 6 s. The carrier gas was He at 2.5 mL min^{-1}
Air, gas[135]	Isoprene Monoterpenes	Gas chromatograph HP 6890 (Agilent Technologies) and a Pegasus III TOF-MS (LECO).	Liquid nitrogen cooled gas jet midpoint modulator.	**HP-5** capillary column 30 m × 0.32 mm i.d. 0.25 μm d_f (non-polar phase)	**BP50** column (SGE, Ringwood, Australia)	The oven temperature program: first column 40 ^{o}C (for 0.5 min) to 200 ^{o}C (held for 10 min) at a rate of 5 ^{o}C min^{-1}; the second column from 55 ^{o}C (for 0.5 min) to 215 ^{o}C (held for 10 min) at a rate of 5 ^{o}C min^{-1}. The carrier gas was He.
Methods development[136]	n-alkanes from a diesel mixture	Gas chromatograph Agilent 6890N, (Agilent, US).	CO_2 duel jet modulator (Thermo, Italy).	**Solgel-wax** capillary column 30 m × 0.25 mm i.d. 0.25 μm d_f	**BPX50** column 2 m × 0.10 mm i.d. 0.10 μm d_f. (solgel-wax)	The oven temperature program: 50 to 250 ^{o}C at 1 ^{o}C min^{-1} The modulation period was 20 s. The carrier gas was He at 30 cm s^{-1} linear flow rate.
Methods development[84]	PAHs Pesticides Chlorinated hydrocarbons Phthalates Haloethers PCBs	Gas chromatograph system with 5975 MSD Mass Spectrometer (Agilent Technologies Inc.).	Everest LMCS longitudinal modulator (Chromatography Concepts, Doncaster, Australia).	**HP-5MS** capillary column 30 m × 0.25 mm i.d. 0.25 μm d_f (5% phenyl methyl polysilphenylene siloxane phase)	**DB-Wax** column 1 m × 0.1 mm i.d. 0.1 μm d_f	The oven temperature program: 50 to 250 ^{o}C at 2.5 ^{o}C min^{-1} with a modulation period of 6 s. The carrier gas was He at 2.56 mL min^{-1}

	n-alkanes					
Modelation[78]	2,3 butanediol 1-octanol nonanal 2,6-dimethylphenol 2,6-dimethylaniline. C_{10}-C_{11} fatty acid methyl ester (FAME)	Gas chromatograph 6890 N Agilent Technologies (Little Falls, DE, USA) with FID.	Thermal modulator system (LECO, St. Joseph, MI, USA).	**Rtx-1** capillary column 30 m × 0.25 mm i.d. 0.25 µm d_f **Rtx-1701** capillary column 20 m × 0.18 mm i.d. 0.20 µm d_f (14% cyanopropylmethyl/14% phenylmethylpolydimethylsiloxane).	**Rtx-1701** column 2 m × 0.18 mm i.d. 0.20 µm df (14% cyanopropylmethyl 14% phenylmethylpolydimethylsiloxane).	The oven temperature was hold up at 100 ^{o}C. The carrier gas was He.
Air, aerosols[137]	n-alkanes PAHs	Gas chromatograph 7890A Agilent (Santa Clara, USA) equipped with a LECO Pegasus® 4D TOFMS system (LECO, St. Joseph, MI, USA).	Thermal modulator.	**HP-5** capillary column 29m×0.25mm i.d. 0.25 µm d_f	**RTX-17** column 0.79m×0.1mm i.d. 0.1µm df	The oven temperature program: first column 50 ^{o}C (5min) to 260 ^{o}C (15 min) at a rate of 5 ^{o}C min^{-1}; the second column from 70^{o}C (5min) to 280 ^{o}C (15 min) at a rate of 5 ^{o}C min^{-1}. The carrier gas was He.

Figure 1: Schematic diagram for the separation process in comprehensive GC × GC.