

## Multidimensional gas chromatography beyond simple volatiles separation

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Multidimensional separation in gas chromatography (MDGC) plays an important role in chemical analysis. This review presents selected literature on MDGC development and examples of the range of functionality reported for MDGC methods over the past 2 decades. With the most obvious advantage of providing much greater capacity for resolving constituents of a sample, MDGC extends analytical efficiency to a more substantial molecular coverage, combined with operational flexibility. But by judicious choice of implementation method, important chemical information relating to the sample, its components, potentially physico-chemical properties, and improved capacity for absolute identification may be realised. Sample-to-sample comparison is improved, and sample characterisation is facilitated especially when MDGC is combined with the informing power of modern mass spectrometry. Innovative MDGC arrangements allow high resolution coupled with spectroscopy and alternative bioassays, and delivers molecular elucidation in ways that are beyond just simple analysis of volatiles.

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### I. Introduction

The chromatographic method has been used for over a century to separate mixtures, and to identify and quantify their components. Today, it is an essential tool for accurate structural and functional determination of individual sample components, as opposed to bulk methods such as fractional crystallisation and distillation techniques which provide low resolution chemical separation. In 1952 the Nobel Prize for chemistry was awarded to A. J. P. Martin & R. L. M. Syngle for their work on partition chromatography; Martin addressed the application of multidimensional chromatography (MDC) for amino acid separation, and the possible use of vapour as a mobile phase, a concept which presaged modern gas chromatography (GC).<sup>1</sup> With high solute diffusion in an inert mobile gas phase, the single capillary GC technique has progressed to its limits for solute separation with excellent peak capacity. The separation mechanism depends upon the chemical nature (*e.g.* polarity or other solute-selective properties) of the column coated stationary phase and the prevailing temperature of the carrier gas.<sup>2–4</sup> Whilst a single column method has served the field admirably, today the multidimensional GC (MDGC) technique is robust and reliable, and has been increasingly applied to the analytical challenges for complex samples that exceed the separation capability of single dimensional (1D) chromatography. The essence of MDGC is the incorporation of multiple sequential

gas phase separations of disparate mechanisms (*i.e.* column selectivities) with a transfer process between ‘dimensions’ that serve to effectively decouple individual retentions. The result for a well implemented MDGC method is greater resolving power, and significantly more peak capacity. The two primary approaches of MDGC involve (i) subjecting a target portion(s) of chromatographic effluent from a first column to a second column separation (*i.e.* the conventional heart-cut MDGC method, which may be termed GC–GC), or (ii) to apply the two-column separation advantage to the entire sample, in a technique called comprehensive two-dimensional GC (termed GC × GC). The latter produces a result not dissimilar to 2D TLC with respect to component coverage in 2D space.

Development of MDGC has evolved in the past few decades to encompass assemblies of precision devices such as microfluidic switches, better gas flow control, and improved fast responding detection methods. The techniques of conventional MDGC and GC × GC have been reviewed in the past (Table 1), with respect to technical design, applications, operational control and data handling. The present report is intended to present approaches to novel molecular-based information available from the advent of MDGC, conceptual studies and applications, in addition to providing our perspectives on future MDGC innovations beyond simple volatiles separation.

### II. Instrumentation for MDGC

With refinements to contemporary devices that enable effluent switching, solute modulation, highly precise control of flows

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**Table 1** Major reviews on MDGC approach in the past decade

Focus of study	Title of article
General aspects in both MDGC and GC × GC	Multidimensional GC <sup>5</sup> Multidimensional GC: fundamental advances and new applications <sup>6</sup> Recent advances in flow-controlled multidimensional GC <sup>7</sup>
General aspects in GC × GC	A new dimension in separation science: comprehensive two-dimensional GC <sup>8</sup> Comprehensive two dimensional GC review <sup>9</sup> Comprehensive two-dimensional GC-mass spectrometry: a review <sup>10</sup> Recent developments in comprehensive two-dimensional GC <sup>11–14</sup>
Optimisation in GC × GC	Optimisation aspects of comprehensive two-dimensional GC <sup>15</sup>
General aspects in MDGC	Heart-cutting multidimensional GC: a review of recent evolution, applications, and future prospects <sup>16</sup>
Chemometrics in GC × GC	Interpretation of comprehensive two-dimensional GC data using advanced chemometrics <sup>17</sup> Review of chemometric analysis techniques for comprehensive two dimensional separations data <sup>18</sup> Features for non-targeted cross-sample analysis with comprehensive two-dimensional chromatography <sup>19</sup> Chemometrics in comprehensive multidimensional separations <sup>20</sup>
GC × GC in food analysis	Potential of comprehensive chromatography in food analysis <sup>21</sup> Multidimensional chromatography in food analysis <sup>22</sup>
GC × GC in metabolomics analysis	New advances in separation science for metabolomics: resolving chemical diversity in a post-genomic era <sup>23</sup>
GC × GC in petroleum analysis	Comprehensive multidimensional separations for the analysis of petroleum <sup>24</sup>
GC × GC in anti-doping analysis	Comprehensive two-dimensional GC applied to illicit drug analysis <sup>25</sup> Application of comprehensive two-dimensional GC to drugs analysis in doping control <sup>26</sup>
MDGC and GC × GC in environmental analysis	A review of environmental toxicant analysis by using multidimensional GC and comprehensive GC <sup>27</sup>
GC × GC in environmental analysis	Comprehensive two-dimensional GC in environmental analysis and monitoring <sup>28</sup> GC × GC-MS hyphenated techniques for the analysis of volatile organic compounds in air <sup>29</sup>

and inertness of valves, MDGC configurations have been introduced for sophisticated gas phase chromatographic analysis. Fig. 1A and B illustrate MDGC implementation, comprising heart-cut MDGC (GC-GC) and GC × GC arrangements, respectively. Modulation serves the function of transferring compounds from <sup>1</sup>D to <sup>2</sup>D, collecting and concentrating small zones at the end of <sup>1</sup>D that are suited for very fast separation on the <sup>2</sup>D column. This process may occur every e.g. 1–8 s. Since the first demonstration in 1991 of GC × GC using resistive heating modulation,<sup>30</sup> development of various modulators including thermal/cryogenic, valve-based and flow modulation, as well as their applications have been extensively reviewed.<sup>6,7,9,31</sup>

Microfluidic technology such as Agilent capillary flow technology (CFT), and the SGE SilFlow device can precisely manipulate effluent switching in MDGC operation and permit multiple column coupling with excellent inertness and minimal dead volume.<sup>5</sup> This allows MDGC analysis in a chip-based analytical platform which is best suited for field analysis.<sup>32–36</sup> Fluid mechanics, mass balance, and system behaviour of the monolithic microfluidic Deans switch in GC was studied by Boeker *et al.*<sup>37</sup> Correction derived from the Hagen-Poiseuille equation counteracted flows within microchannels of the device, to provide accurate effluent switching to a mass spectrometry (MS) vacuum outlet and an olfactory port. Development of a high speed Deans switch was reported for fast duty cycle GC × GC modulation capable of generating narrow pulses

(<50 ms) of primary effluent with a 2 mL min<sup>-1</sup> second column flow for better analytical sensitivity.<sup>38</sup> Using a reverse flush arrangement combining two CFT switches to perform differential flow modulation, Griffith *et al.*<sup>39</sup> observed higher sample loading capacity with a 10-fold decrease in tailing in the GC × GC analysis, as compared to forward flush modulation.

The open-tubular capillary column has completely replaced the conventional packed GC column for analytical studies since the 1980s.<sup>40</sup> Micro-bore ( $\leq 0.18$  mm internal diameter) columns are gaining popularity for high speed analysis.<sup>41</sup> Numerous novel stationary GC phases such as ionic liquids,<sup>42,43</sup> monoliths,<sup>44</sup> cyclodextrin derivatives,<sup>45</sup> liquid crystals or metal organic framework<sup>46–48</sup> have been introduced. Recent development of dithienyl benzothiadiazole that exhibits specific intermolecular interactions such as heteroatom contacts or  $\pi$ - $\pi$  interactions has been reported for GC application.<sup>49</sup> Polyethylene-glycol-based sol-gels containing cyclodextrin or calix[6]arene derivatives<sup>50</sup> were incorporated as GC stationary phases to provide enantioselective separation at higher thermal stability. Ionic liquid columns that possess unique selectivity have been favourably used in MDGC analysis for samples such as diesel,<sup>51</sup> *Clausena lansium Skeels* leaves,<sup>52</sup> and commercial perfume.<sup>53</sup> It is to be anticipated that such phases will increasingly be used for multidimensional GC analysis, providing useful and potentially unique separation that might improve the extent of orthogonality of the phase combination.

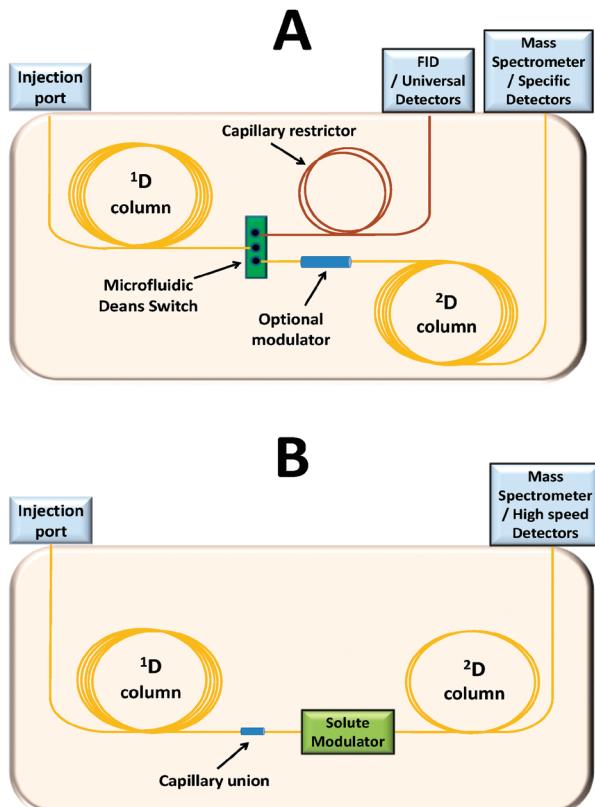


Fig. 1 Contemporary devices in (A) heart-cut MDGC (GC-GC) and (B) GC  $\times$  GC systems.

Despite the popularity of McReynold's constants and Gibbs free energy scales, the Abraham's solvation parameter model has been widely applied to characterise the interaction of gas-phase solutes in the GC stationary phases.<sup>54</sup> This classification explains the solute mass transfer interaction with the phase based on several specific interactions namely hydrogen-bond, electron lone-pair interactions, dipole moment, cavity formation and dispersion.<sup>55</sup> Approximating the retention time of solutes in four GC  $\times$  GC columns sets has also been reported using Abraham's solvation parameter model using retention data from standard single-column temperature-programmed separations.<sup>56</sup> The model was simplified by applying the temperature-averaged values of the stationary phase descriptors, which attained standard errors of 1% and 5% in both <sup>1</sup>D and <sup>2</sup>D respectively. This allows some measure of prediction of the 2D separation to be realised.

Development of various MDGC approaches can be conveniently reduced to considerations of column dimensions, using a variety of ancillary devices, and different implementation strategies (Fig. 2). The capillary column largely determines how the different chromatographic stages (dimensions) provide access to respective MDGC methods that enhance the resolving power of the system. A cryo-trapping step is usually applied, after the heart-cutting process by Deans switching or sometimes by valve-based switching, as shown in Fig. 1A, in order to re-focus the transferred analyte and reduce peak dispersion that arises

on the first column. For example, Fig. 2 indicates that preparative MDGC analysis may be achieved using coupling of two wide bore columns – this gives larger sample loading capacity.<sup>52,57-59</sup> A shorter normal bore <sup>1</sup>D column was used for high temperature (HT) GC  $\times$  GC and GC-GC ( $> 300$  °C) to resolve high boiling solutes.<sup>60-63</sup> Further column combinations incorporating three or more GC columns allow ultrahigh resolution analysis, namely smart 3D micro-GC,<sup>34</sup> comprehensive 3D GC,<sup>51</sup> and preparative 3D GC,<sup>52,64</sup> integrated/switchable GC-GC with GC  $\times$  GC,<sup>65,66</sup> and hybrid (sequential) GC  $\times$  GC-GC.<sup>67</sup>

### III. Expanded peak capacity in MDGC corresponds to improved sample & solute characterisation

MDGC performance has been determined using a number of proposed metrics. Since the plate height/theoretical efficiency strictly refers to a single peak in the chromatogram, the peak capacity ( $n_c$ ) concept was introduced by Giddings<sup>68,69</sup> in order to determine the overall number of resolvable peaks in the chromatographic analysis;  $n_c \approx 1/4(N^{1/2})\ln(V_{max}/V_{min})$ , where  $N$  is the theoretical plate number,  $V_{max}$  is the maximum elution volume, and  $V_{min}$  is the minimum elution volume, which can be interpreted in terms of retention times. In modern high resolution GC,  $n_c$  is defined as the maximum number of components that can be separated at a specified resolution ( $R_s$ ; which is assumed as 1) within a given separation time window ( $\Delta t$ ), expressed as  $n_c = \Delta t/wR_s = \Delta t/4\sigma R_s$ , where  $w$  is the width at the base of the peak,  $\sigma$  is the Gaussian standard deviation.<sup>70</sup> Higher  $n_c$  values indicate higher separation capability; more compounds can be uniquely located within the time window.

Statistical-overlap theory (SOT) was subsequently proposed and tested by Giddings and Davis<sup>71-76</sup> in order to predict the number of observable peaks and to statistically describe the overlap in both 1D and 2D chromatographic results. The SOT illustrates the probability of single peak formation,  $p_i$ , in  $i$ -th separation as  $p_i = e^{-2m/n}$ , where  $m$  is the number of components in the sample.<sup>72,73</sup> SOT simulation<sup>76</sup> demonstrated that separation efficiency by 1D GC was insufficient to produce single-component peaks in complex samples, postulating the need of 2D GC with larger peak capacity. The importance of peak saturation,  $\alpha = m/n$ , was shown in the point-process SOT and indicates that the peak capacity in the system must greatly exceed the number of components ( $\alpha \ll 1$ ) to separate a mixture.<sup>75</sup> Davis and Carr<sup>77</sup> further discussed a metric of effective saturation,  $\alpha_e$ , through SOT for the comparison in both <sup>1</sup>D and <sup>2</sup>D separations, defined as  $\alpha_{e,1D} = m/(^1R_s ^1n)$ , and  $\alpha_{e,2D} = m/(^1R_s ^2R_s ^2n)$  respectively.

When extended to GC  $\times$  GC, the total  $n_c$ ,  $n_{total}$ , ideally becomes the product of peak capacity generated in the two individual chromatographic dimensions maximised by orthogonal selectivities, which is expressed as  $n_{total} = ^1n \times ^2n$ , where  $^1n$  and  $^2n$  are peak capacities in <sup>1</sup>D and <sup>2</sup>D, respectively. However,  $n_{total}$  is often overestimated when applied in practice,

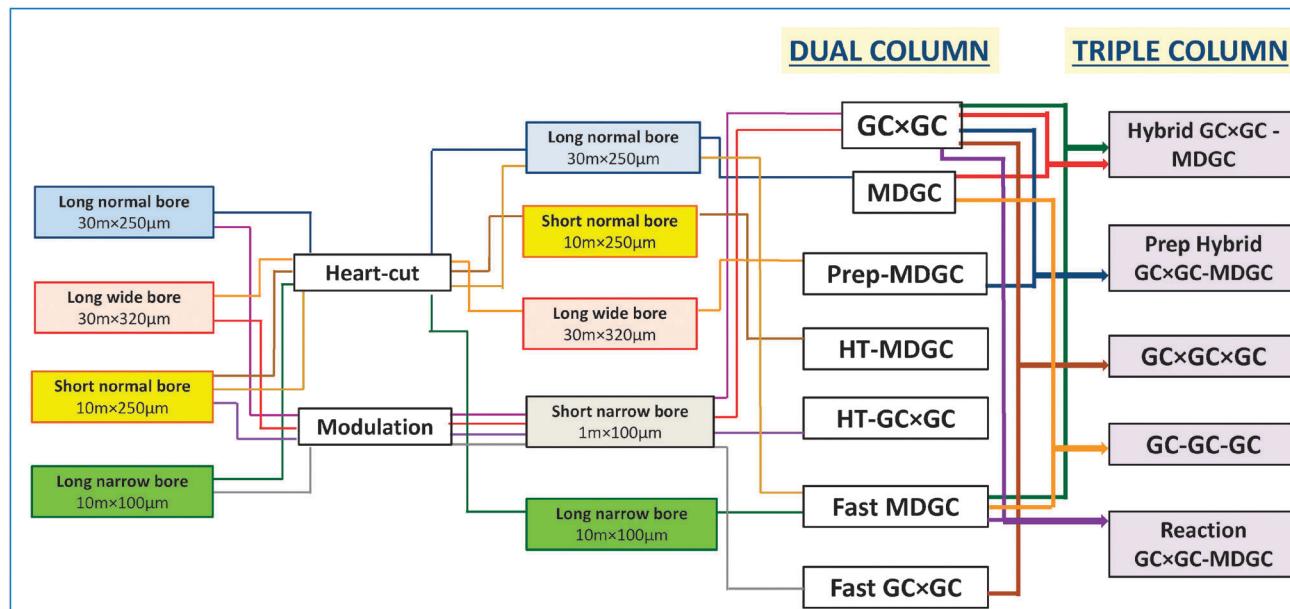


Fig. 2 Route map of column dimensions which may be coupled for different MDGC approaches.

due to several aspects such as under-sampling from  $^1\text{D}$  separation.<sup>78</sup> The effective 2D peak capacity was then proposed according to SOT as  $n_{\text{total}'} = n_{\text{total}} \times \langle \sigma \rangle / \langle \sigma^* \rangle$ , where  $\langle \sigma^* \rangle$  is the average standard deviation of peaks along  $^1\text{D}$  as observed in 2D separation; so  $\langle \sigma^* \rangle / \langle \sigma \rangle$ , later denoted  $\langle \beta \rangle$ , is referred to first-dimension peak broadening factor caused by under-sampling of the  $^1\text{D}$  peak. In the box-counting method or surface coverage metric model, the practical peak capacity is proposed as  $n_{\text{total}'} = n_{\text{total}} \times \sum \text{bins} / P_{\text{max}}$ , where  $\sum \text{bins}$  is the number of bins in the 2D plot containing data points,  $P_{\text{max}}$  is the total peak capacity obtained as the sum of all bins.<sup>79</sup> Recently  $\langle \beta \rangle$  and fractional coverage,  $f_c$  (equivalent to  $\sum \text{bins} / P_{\text{max}}$ ) has been considered,<sup>80–82</sup> by re-defining the effective peak capacity as  $n_{\text{total}'} = n_{\text{total}} \times f_c / \langle \beta \rangle$ . Nevertheless, such a metric derived from the surface coverage approach requires further study since the binning estimation is not related to the actual peak capacity in each separation dimension.

#### IV. Orthogonality of coupled column phases – getting most from the experiment

Phase orthogonality in MDGC separation is a general guideline for column set selection in order to maximise solute resolution. Determination of the degree of orthogonality should correspond to efficiency of use of the separation space as reflected by peak capacity and analytical speed.<sup>83</sup> The peak position in a  $\text{GC} \times \text{GC}$  separation using different column arrangements and elution temperatures  $T_e$  can be predicted.<sup>84</sup> SOT simulation<sup>82,85,86</sup> estimated a maximum value of 63% for 2D geometric coverage in an ideally orthogonal separation, thus the practical orthogonality,  $O$ , was generally defined as  $O = (\sum \text{bins} - \sqrt{P_{\text{max}}}) / 0.63P_{\text{max}}$ .<sup>79</sup>

This definition was modified by Watson *et al.*<sup>86</sup> to maximise the information content, and proposed  $O = (\sum \text{bins} - P_{\text{max}}) / (0.63P_{\text{max}}^2 - P_{\text{max}})$ . Besides various surface coverage concepts,<sup>79,87</sup> other different metrics such as informational theory,<sup>88,89</sup> peak spreading angle,<sup>90</sup> practical peak capacity,<sup>79</sup> fractal dimension,<sup>91</sup> correlation coefficients,<sup>88,92</sup> nearest-neighbour distances<sup>93,94</sup> and space occupation<sup>84,95</sup> have been proposed as measures of orthogonality. Limitations of some of these approaches have been discussed,<sup>80,96,97</sup> suggesting the unsuitability of the correlation coefficient for orthogonality measurement, dependency of partitioning of the separation space based on surface coverage, and weak robustness for data with statistically smaller number. The correlation of component retention in both 1D and 2D separation space has recently been re-evaluated for estimation of orthogonality. Zeng *et al.*<sup>96</sup> introduced the metrics of coverage percentage of bins,  $C_{\text{pert}} = \sum \text{bins} / (0.63 \times n_{\text{total}}^2)$ , and correlation of the 2D peak distribution,  $C_{\text{peaks}} = 1 - R^2$ , re-defining the orthogonality as  $O = C_{\text{pert}} \times C_{\text{peaks}}$ . This approach employs preceding methods based on bin coverage whilst also using raw data to estimate correlation. Hence orthogonality can be reliably studied. A 3D system ( $\text{GC} \times \text{GC} \times \text{GC}$ ) was described previously, incorporating a DB-5 (apolar phase), a Wax (polar phase), and an ionic liquid (unique selectivity phase) with 3 different sequential stages with solute modulation periods successively reduced from 20 min to 0.2 s.<sup>98</sup> To date, studies reporting definitive considerations of orthogonality of analysis employing multiple coupled stationary phase dimensions are relatively few. However it is apparently tempting for authors to claim their chosen conditions lead to orthogonal separations. In order to achieve maximum resolution, progress in understanding the orthogonality concept at the level of detailed molecular parameters is still intriguing.

## V. Selected applications of MDGC

In addition to fingerprinting for biomarker discovery and correlation, sample profiling with classification for known compound confirmation and behaviour across different samples is of interest. This includes samples challenged by chemical and physical processes in order to study changes in *e.g.* bioactivity and molecular dynamics, reported using various MDGC approaches. The overall field of MDGC applications may be compartmentalised according to the specific research focus as listed in Table 2. Here we consider an ultra-complex sample to be a sample consisting of a number of components in a mixture that significantly exceeds the peak capacity of GC × GC, *e.g.* a crude oil. Selected examples follow:

### Characterisation of unresolved complex mixture

The ‘unresolved complex mixture (UCM)’ as observed in petroleum analysis or atmospheric organics comprises many thousands of chemical constituents; it is revealed as a rising-then-falling baseline or “hump” of co-eluting compounds in a 1D gas chromatogram.<sup>99,100</sup> UCM analysis has been a challenge for decades. Boer and co-workers<sup>101,102</sup> in the 1980s reported a coupled-column petrochemical analyser incorporating 3 different packed columns using multiple heart-cut stages, which enabled automated group type clustering of paraffins, naphthenes and aromatics but was insufficient to resolve compounds within individual chemical groups. Two approaches to the analysis of UCM-containing samples based on capillary MDGC include (i) taking individual narrow H/Cs with high efficiency second column elution in an attempt to provide a measure of resolution, or (ii) subject the whole sample to GC × GC analysis, which uses a lower resolution 2D column, but provides a unique structured retention in 2D space which may allow sample components to be teased apart based on the chemical nature of UCM compounds.<sup>99,103–105</sup> Fig. 3 contrasts analysis of UCM of bitumen extract obtained using 1D-GC and GC × GC separation.<sup>99</sup> An interesting phenomenon is the structured nature of the 2D plot (Fig. 3). Relative positions of components in 2D space are a function of the phases employed in the experiment. Whilst boiling points (B.P.) and ‘polarity’ of compounds, and phase composition are known to play key roles in determining relative positions, the separation mechanisms of many isomeric compounds remain unclear; *e.g.* reasons for different C<sub>n</sub> naphthalene isomers exhibiting particular positions in the 2D plot. The revelation of resolved components especially into different chemical classes in Fig. 3B provides immeasurably improved knowledge of sample composition for such samples. Since chromatography developments largely deal with improving component resolution, the interest in accessing GC × GC is understandable.

Similarly, a military fog oil sample derived from petroleum distillate was better characterised by using GC × GC coupled with time-of-flight mass spectrometry detection (TOFMS).<sup>106</sup> Greater resolution on the early eluted hump region revealed that the fog oil consists of 90% aliphatic compounds ranging from C10 to C30 with naphthenes dominating, whilst monoaromatic species and other polycyclic aromatic groups are also present. Prior Ag<sup>+</sup> fractionation was applied and further GC × GC data suggested the lack of unsaturated aliphatic compounds

Table 2 Research focus for application of various MDGC approaches

Research focus	Proposed technique									
	Prep-GC- GC × GC	HT-GC- GC	HT-GC × Fast GC-GC	Fast GC × GC	Chiral GC-GC	Hybrid GC × GC	Hybrid GC-GC	GC × GC × GC-GC	GC × GC × GC-GC	Reaction GC × GC-GC
Identification of known compounds	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Characterisation of unknown (complex) samples <sup>104,115–126</sup>	✗		✗	✗	✗	✗	✗	✗	✗	✗
Physical-chemical study of known compound <sup>1127–134</sup>			✗	✗	✗					
Cross sample classification <sup>135–141</sup>				✗	✗					
Sample authentication <sup>142–146</sup>										✗
Chemical profiling of ultra-complex samples <sup>148,147–155</sup>										
Explicit confirmation of known compound <sup>156–160</sup>										
Explicit confirmation of known compound(s) in ultra-complex sample										

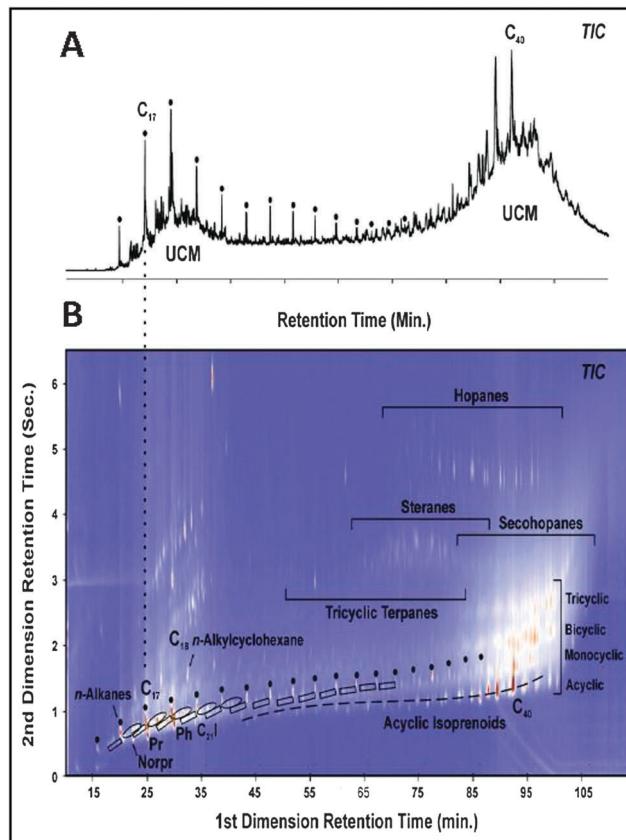


Fig. 3 TIC chromatogram of the bitumen extract analysed using (A) GC-MS, (B) GC × GC-MS; extracted from ref. 123.

contained in fog oil. Notwithstanding the better resolution of GC × GC, this application demonstrated that peak capacity was still insufficient for total component separation. Oil sands process-water (OSPW) is an enriched complex material of serious concern due to possible environmental effects of their toxic constituents. Monitoring of the chemical changes for OSPW, especially the acid-extractable organic matter largely comprising naphthenic acids (NA), is requisite since the toxicity of the stored water decreases with time.

A GC × GC-TOFMS approach<sup>107–110</sup> (Fig. 4) shows a contour plot in which various adamantane carboxylic acids in OSPW were distinguished.<sup>107</sup> A range of diamantane, methyl- and dimethyl-diamantane, diamantane ethanoic, methyl- and dimethyl-diamantane ethanoic and higher alkylated diamantine acids were observed in OSPW NA, with distributions of isomeric diamantane acids readily displayed by mass chromatography of selected ions. Only the major compounds could be identified, with synthesis confirming the proposed component identities. Again it was apparent that the major components eluted on a background of unresolved minor components. The described GC × GC method was credited for providing better reclamation/remediation strategies for NA as well as for facilitating identification of the sources of NA in contaminated surface waters.

Atmospheric UCM from urban sites was studied using different multidimensional approaches. Results<sup>103,111–113</sup> showed excellent GC × GC separation of aromatic compounds using an

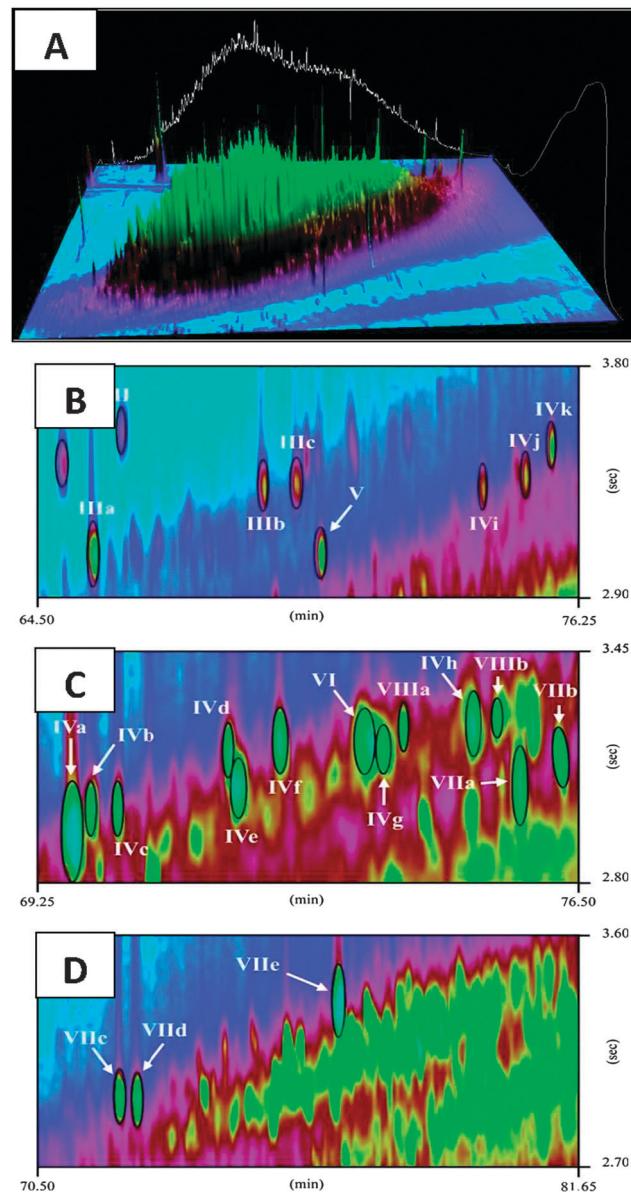


Fig. 4 GC × GC-TOFMS contour plot and mass spectra of selected adamantane carboxylic acids ((A) TIC; (B)  $m/z$  134 + 135; (C)  $m/z$  163 + 193; (D)  $m/z$  177 methyl esters) in OSPW, peak labels refer to the original manuscripts; extracted from ref. 120.

apolar–polar column set, revealing the complexity of organic composition and temporal variability of atmospheric aerosols. Trace analysis of polycyclic aromatic hydrocarbons (PAHs) and their derivatives (oxygenated, nitrated, and methylated PAHs) in particulate samples was performed using thermal desorption-GC × GC coupled with triple quadrupole tandem mass spectrometry (MS/MS) with selected reaction monitoring (MRM) mode.<sup>114</sup> This is one of the first examples of MS/MS mode used for GC × GC separations.

By removing matrix interferences, approximately 0.01 pg PAH products was successfully determined in diesel exhaust ranging from accumulation-mode particles (100–180 nm) to nanoparticles (18–32 nm). Hyphenation of GC × GC with single-photon soft

ionisation (SPI)-TOFMS produced a three dimensional array ( $\text{GC} \times \text{GC} \times \text{MS}$ ) for characterising the constituents originating from mineral oil diesel blended with biodiesel,<sup>161</sup> which made it possible to extend to the separation of isobaric and even isomeric compounds.<sup>162</sup> GC  $\times$  GC analysis in urban air samples depicted a large proportion of aromatic volatile organic carbon, with clear consequences for ozone formation.<sup>119</sup> The discrepancy of over-predicted measurement of certain reactive tropospheric carbon species can be minimised for successful and accurate prediction of pollution episodes.

### Reaction MDGC for study of molecular behaviour

High resolution isomeric analysis by MDGC offers the possibility of new insights in studying molecular dynamic (physical-chemical) behaviour such as enantiomerisation, epimerisation, isomerisation and decomposition. Determination of the reaction barrier and rate constants can be characterised through interpretation (simulation; first principles chemical change) of plateau formation or peak broadening arising from the interconversion of the isomeric, epimeric, or enantiomeric analytes during the single chromatography (1D) process.

Stopped-flow GC-GC incorporating chiral selective columns was demonstrated for evaluating the enantiomerisation barrier of atropisomeric polychlorinated biphenyls (PCBs), dimethyl-2,3-pentadienedioate, 1-chloro-2,2-dimethylaziridine, and 3,4-ditert-butyl-1,3,4-oxadiazolidine components.<sup>130</sup> The enantiomers of interest were first separated quantitatively on a Chirasil-Dex primary column ( ${}^1\text{D}$ ) with FID as monitoring device; either the first or the second eluted enantiomer was subsequently heart-cut to a second column ( ${}^2\text{D}$ ) where enantiomerisation was effected by oven heating in the absence of carrier gas in the  ${}^2\text{D}$  column for a given contact time. The resultant enantiomers were separated on the third dimension column. This approach provides rate constants of the dynamic chromatographic experiment through resolution on the chiral stationary phase.<sup>131</sup>

Interconversion of *E*- and *Z*-oximes has been studied using GC  $\times$  GC to determine the instantaneous ratio of the individual isomers.<sup>128,129,132</sup> In such an array – the dynamic GC  $\times$  GC (DGC  $\times$  DGC) technique – molecular interconversion occurs on both  ${}^1\text{D}$  and  ${}^2\text{D}$  columns, but the short length of, and retention on,  ${}^2\text{D}$  promotes little interconversion. For an achiral phase, two spots are seen in 2D space, with an elongated ‘tail’ extending from the peak corresponding to, for example, isomer *E* that converts into isomer *Z*. In this case, the tail has the same  ${}^2\text{D}$  time as *Z*, but is separated from the primary *Z* peak. In a subsequent study applied to chiral oximes,  $\text{R}^*\text{C(H)=NOH}$ , a novel column arrangement comprising of a  ${}^1\text{D}$  dual column ensemble (enantioselective + polar wax) that separates *E* enantiomers (well) and *Z* enantiomers (poorly), with a wax  ${}^2\text{D}$  column to separate *E* and *Z*, was tested. This leads to a peak profile as shown in Fig. 5,<sup>127</sup> describing the kinetics and thermodynamics of the interconverting molecules during chromatographic elution, depicting the thermodynamic Gibbs free energy of the *E/Z* isomerisation of oximes. A 1D GC system gave the result in Fig. 5B, which does not reveal the individual *E* and *Z* isomer distribution. The modulation process and second dimension

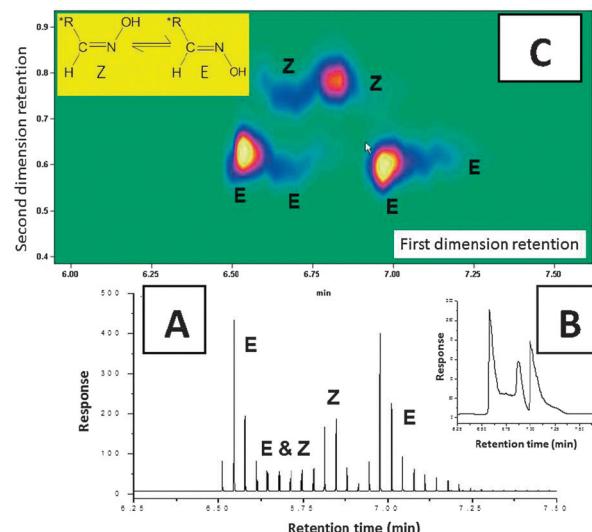
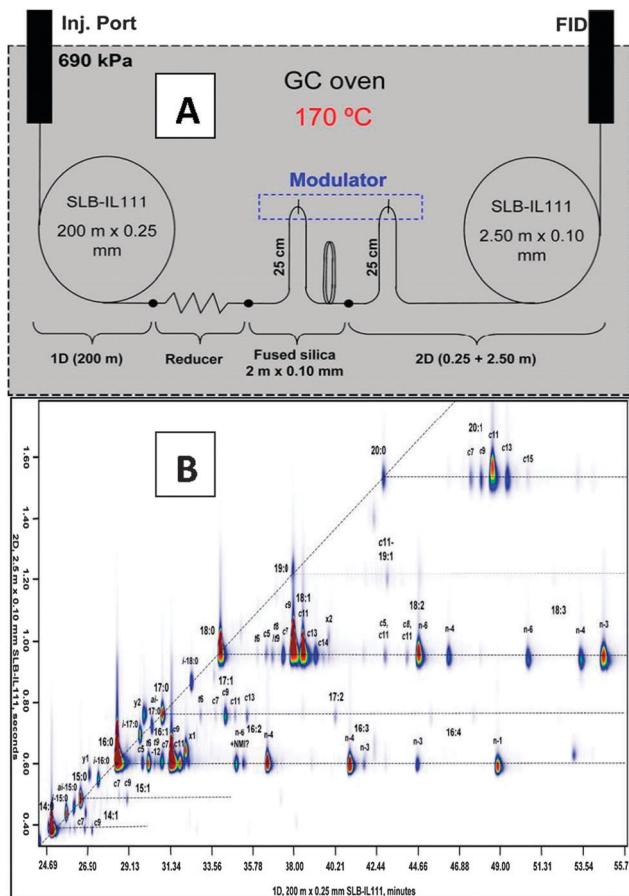


Fig. 5 (A) Modulated GC  $\times$  GC chromatogram, (B) conventional 1D GC chromatogram, (C) 2D contour plot for molecular interconversion of chiral oxime compounds revealed by DGC  $\times$  DGC analysis; extracted from ref. 127.

separation effectively deconvolutes the  ${}^1\text{D}$  result at each indicated  ${}^1\text{D}$  time-point to provide *E* and *Z* separation, as shown in Fig. 5A. Presentation in the GC  $\times$  GC 2D space now clearly displays the full chromatographic story. Isomer interconversion effected by various activation parameters including prevailing temperature, retention time, and the phase type during chromatography can be characterised.<sup>128,132</sup> MDGC is the only approach able to provide unique speciation of the individual isomers.

Multiphase reactions performed on-column, such as substance metathesis, including hydrogenation, has been applied in GC analysis which is useful for selective transformations in analytical applications and for compound structure elucidation. Trapp *et al.*<sup>163</sup> reported on-column catalysis by coupling miniaturised reactors with highly selective catalysts such as a Pd nanoparticle micro-capillary and combined GC techniques. Development of capillary reaction with continuous hydrogenation was employed in a multi-column GC  $\times$  GC design for reduction of unsaturated fatty acid methyl esters (FAME) to their fully saturated forms and subsequent  ${}^2\text{D}$  separation (Fig. 6).<sup>164</sup> Rather than employing two GC columns of different polarities or using different elution temperatures, the separation in the two-dimensional space is achieved by altering the chemical structure of selected analytes between the two separation dimensions, eliminating the overlap between polyunsaturated fatty acids (PUFAs) with different carbon chain lengths on the second column. Here, the abscissa plots the elution time of the total sample, which comprises both saturated and unsaturated FAME; on the polar  ${}^1\text{D}$  column, unsaturated compounds elute later than their saturated analogues of a given carbon number. After hydrogenation, the ordinate arranges the FAME into bands corresponding to number of carbons (shown as successive horizontal lines). Thus injected saturated FAME are located on the oblique line; injected unsaturated FAME are shown as later spots on the horizontal lines. On-column derivatisation with various reagents or deuterium carrier would be of interest



**Fig. 6** (A) Schematic system configuration for GC  $\times$  hydrogenated-GC analysis; (B) acquired GC  $\times$  GC contour plot for menhaden oil sample; extracted from ref. 164.

in MDGC applications for separation of highly polar compounds and potentially structure elucidation of organic compounds.

Interestingly, this example uses the same column in both dimensions, and so this is contradictory to the usual requirements for an orthogonal system. However, it is the chemical reaction that provides correlation of peak position with chemical structure.

### Cross-sample classification using MDGC

Chiral GC-GC and GC  $\times$  GC analysis disclose enantiomeric species in a sample regardless of the background matrix through physical resolution of matrix and enantiomer. Enantioselective GC  $\times$  GC-TOFMS enables precise analysis of small quantities of amino acids in astrophysically relevant achiral ice mixtures in order to measure statistically significant enantiomeric excesses (e.e.).<sup>136,165</sup> The e.e. calculated via abiotic cosmic ice simulation supported the origin of biomolecular asymmetry on Earth, and that of the protosolar nebula has indeed been formed in a region of massive star formation. The e.e. determined by chiral GC-GC coupled with combustion/pyrolysis-isotope ratio MS (IRMS) has been applied for sample authentication particularly in food products of citrus<sup>166</sup> and raspberry,<sup>167</sup> essential oil of lime<sup>168</sup> and lavender,<sup>169</sup> and natural blackberry flavour.<sup>170</sup>

Effective separation by MDGC, especially GC  $\times$  GC hyphenated with MS, offers high-dimensional datasets for interpretation of chemical processes and sample treatments. Chemometric interpretation of post-MDGC data has been performed to associate various study goals such as experimental parameter optimisation, data quality improvement, identification and quantification of target chemical components, image processing for product pattern recognition, and multivariate models to correlate chromatographic properties and molecular descriptors.<sup>17–20,171</sup> Non-targeted cross-sample analysis is particularly applied to the study by using various chemometrics features generated from comprehensive two-dimensional chromatography data,<sup>18,19</sup> generally categorised into data-point features, peak features, region features, and peak-region features; relative advantages and disadvantages of these approaches have been reviewed recently.<sup>19</sup> By providing greater coverage of sample composition through various MDGC methods, presumably improved data interpretation is realised.

Pixel-based chemometric methods have been utilised to handle GC  $\times$  GC datasets, prior to hierarchical clustering to distinguish chemically similar samples.<sup>172</sup> Subsequent calculation of Fisher criteria based on the defined clustering was processed in order to identify promising marker compounds. An image processing approach exploiting the GC  $\times$  GC contour plot was demonstrated for unbiased pattern comparison or profiling analyses, with differentiation of volatile patterns from fruits such as apples, pears, and quince fruit.<sup>173</sup> In brief, run-to-run variations among GC  $\times$  GC data have been compensated by Delta2D image warping and then merged into a fusion image yielding a defined and project-wide spot (peak) consensus pattern, which was processed for clustering and pattern comparison algorithms. An alternative classification approach was implemented by Cordero *et al.*<sup>174</sup> combining chromatographic fingerprinting and MS fragmentation pattern similarity criteria. With 411 chromatographic features from 9 hazelnut samples, chemical speciation of the volatiles and sample profiling was extended to known markers whilst their distribution was well correlated to sensory properties, geographical origin, or the effect of thermal treatment on different classes of compounds.

Reichenbach *et al.*<sup>139</sup> reported an informatics method integrated from GC  $\times$  GC-high resolution MS (HRMS) analysis with 18 breast-cancer tumor samples for identifying potential biomarkers for closer examination. Peak-region features as shown in Fig. 7 were employed for processing of GC  $\times$  GC datasets that avoids the intractable problem of comprehensive peak matching by using a few reliable peaks for alignment and peak-based retention-plane windows. This approach proves more comprehensive than using reliably matched peak features and is more selective than region features, and eventually allows classification that matches grading by a cancer pathologist with 78% success in leave-one-out cross-validation experiments. Consistent cliques method was developed later to utilise all pairwise peak matches from multiple chromatograms, searching subsequent maximum cliques to extract reliable features.<sup>175</sup> Nevertheless, it is anticipated that feature generation and matching can be improved by better pre-processing methods and separation of co-eluted peaks in the MDGC analysis.

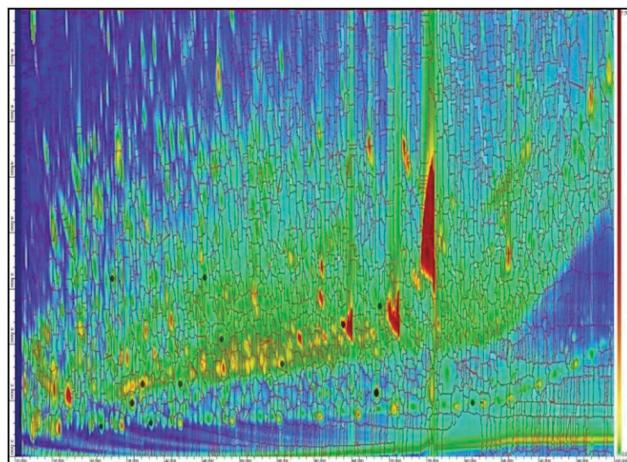


Fig. 7 Cumulative chromatogram for eighteen breast-cancer tumor samples overlaid with the feature template; extracted from ref. 139.

### MDGC analysis with extended molecular and polarity range

Limitations in volatility and polarity of analytes that can be suitably analysed by GC are drawbacks of GC analysis. The molecular application range may be extended through development of high temperature (HT) GC, various derivatisation approaches, and coupling of GC with other chromatographic techniques.<sup>176</sup> Sutton and Rowland<sup>60</sup> reported an assembly of a HT GC-TOFMS system that is capable of rapid (<25 min) analysis for C10 to C100 hydrocarbon boiling point range and full mass spectral data recording up to  $m/z$  1850. Analysis of diverse substrates include long-chain (>C60) *n*-alkanes, *n*-acid methyl esters up to C64, triacylglycerides (TAGs) with molecular and fragment ions in a single analysis, intact wax esters from C40–64, C80 glycerol alkyl glycerol tetraethers, and C33–44 metallated porphyrins was shown without significant thermal degradation of analytes, with MS operated at 430 °C. Mahé *et al.*<sup>177</sup> demonstrated GC × GC elution of linear alkanes up to C-68 (B.P. 641 °C) as well as of highly aromatic hydrocarbons (*e.g.* coronene) by reducing both discrimination and adsorption of high boiling point compounds during the chromatography process. Such analyses are critical for evaluating heavy hydrocarbons particularly in heavy petroleum fractions. The coupling of HT-GC × GC with TOFMS allows for routine analysis of high B.P. compounds which are eluted from the column with oven cycling up to >400 °C.

Coupling of various routine chromatographic approaches such as liquid chromatography (LC), or supercritical fluid chromatography (SFC) to GC permits efficient chemical analysis of a broad range of components, with careful adjustment of conditions due to respective pressure and chemical properties of the diverse mobile phases.<sup>178</sup> Application of comprehensive multidimensional chromatography (MDC) describing multiple coupled systems were reviewed.<sup>21,24,150,179</sup> By employing novel stationary phases as the third dimension, hyphenated GC × GC × GC systems<sup>51,180</sup> were demonstrated, whilst an extended range of olefins in various petrochemical samples was analysed using GC-GC × GC.<sup>181,182</sup> Development of online SFC-GC × GC<sup>24,150,183,184</sup>

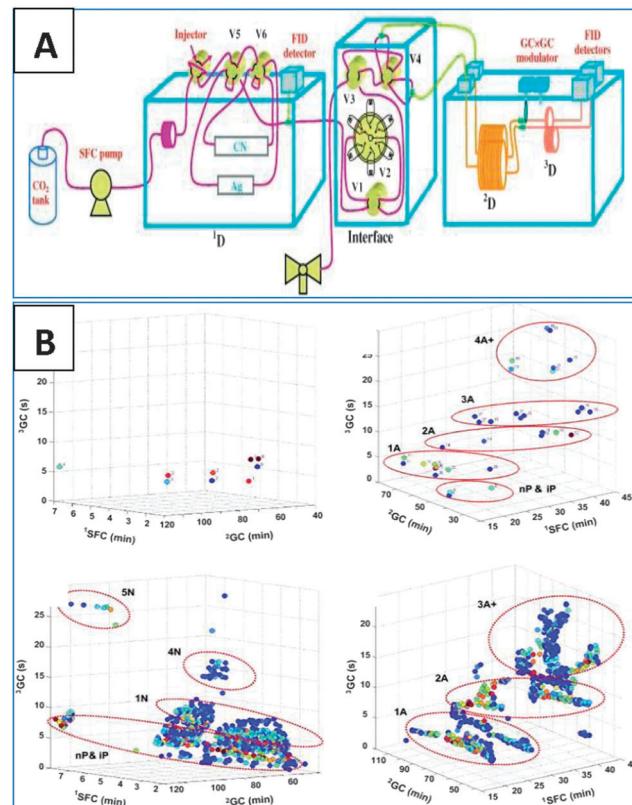


Fig. 8 (A) Schematic diagram of SFC × 2GC × GC-FID system; (B) quantitative 3D plots of different fractions from heavy vacuum gas oil acquired using the above system; extracted from ref. 150.

and SFC × GC × GC<sup>184</sup> as well as online LC-GC × GC<sup>185,186</sup> for oil and food samples analysis was reported recently. The integrated SFC × 2GC × GC<sup>150</sup> approach as shown in Fig. 8 depicts a further implementation in full 3D separation mode with three ‘orthogonal’ dimensions. By storing several SFC fractions inside purpose-designed sampling loops of the interface device, the proposed system enables automated SFC switching/diversion for subsequent HT-GC × GC analysis, rather than employ a real-time or stopped-flow approach.

Vacuum gas oil was then characterised according to the saturated, unsaturated and polar fractions with comprehensive 3D separation as illustrated in Fig. 8. Incorporation of SFC separation provides useful information especially for unsaturated fractions for global enrichment by aromatic ring number with incremented SFC fractions. Although the global 3D space occupation showed more or less diagonal scattering, the proposed approach offers a useful MDGC separation with higher flexibility in terms of column selectivity and system coupling.

### MDGC effluent for physiological profiling

MDGC separation is well-suited to the integration of alternative identification tools with the GC method, such as olfactometry, electroantennographic detection (EAD), nuclear magnetic resonance spectroscopy (NMR), and other detectors for better characterisation of separated chemical species.<sup>187</sup> Gas chromatography-olfactometry

(GC-O) is commonly applied for estimation of the online sensory contribution of single odour active compounds to overall sensory perception of a sample, by separation from other volatiles in the sampled mixture.<sup>188</sup> A fully computerised eight-way GC-O system has been developed that allows delivery of effluent and individual aromagrams assessment by a panel of eight judges to be obtained simultaneously for one GC analysis. This eight-way multiport GC-O system was compared with GC × GC-TOFMS analyses for the identification of trace odorant constituents.<sup>189</sup> This approach pre-supposes that individual aroma-active compounds are effectively resolved in the GC step. To adequately profile a complex aroma with olfactometry, multiple systems such as GC × GC-TOFMS, GC-GC-O/MS, and 1D GC-O/FID may be proposed for verification of odorants.<sup>190–192</sup> While these studies were highly informative, they require tedious and potentially inaccurate data correlation between multitude systems.<sup>190</sup> To overcome this uncertainty, a hyphenated separation system integrating both GC × GC and GC-GC coupled to simultaneous O/FID and O/MS detection has been introduced, as illustrated in Fig. 9.<sup>65</sup> Such a system delivers sophisticated gas-phase separations through comparative GC × GC and MDGC analyses, and suits volatile and semi-volatile chemical analysis with a significant coverage of sample components present from trace to major amounts.

Sensory characterisation and analysis of aroma mixtures was studied using a GC recombination-olfactometry (GC-RO) approach.<sup>193</sup> With microfluidic flow-switching and cryotrapping operations in-line at the end of the GC column, this approach allows the analyst to isolate and recombine desired components of the mixture by selecting either the compounds, peaks, or sections based on retention time allowing either inclusion or exclusion of different regions or components in a reconstitution step for subsequent sensory analysis. Mixtures of aroma subsets were built and further subjected to olfactometry to characterise the aroma quality of lavender flower using this approach. A MDGC approach permitting a greater chance of individual peak separation with the selected volatile recombination approach should extend this method to further understand the flavour synergism phenomenon.

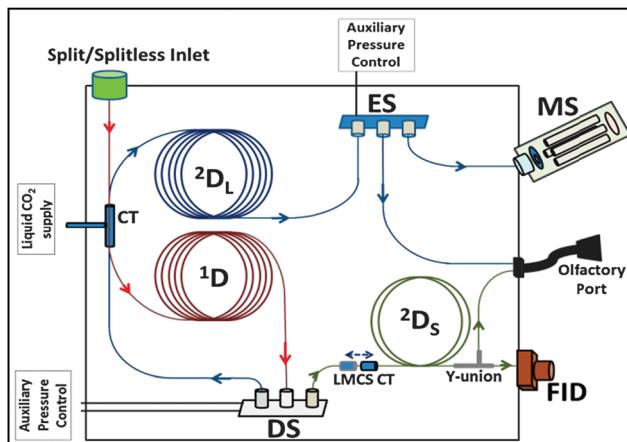


Fig. 9 Instrument schematic of the integrated GC × GC/GC-GC system with flame ionisation, olfactory and mass spectral detections.

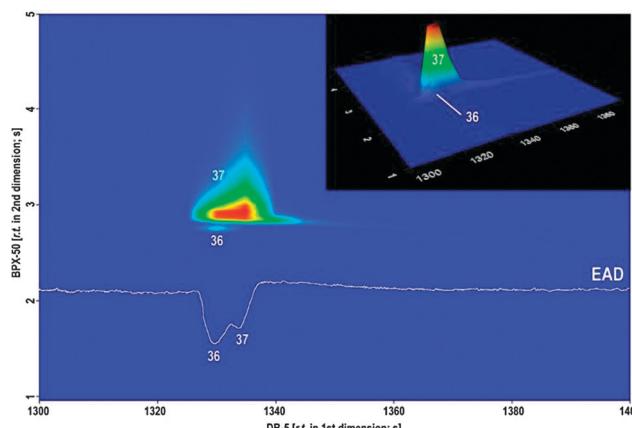
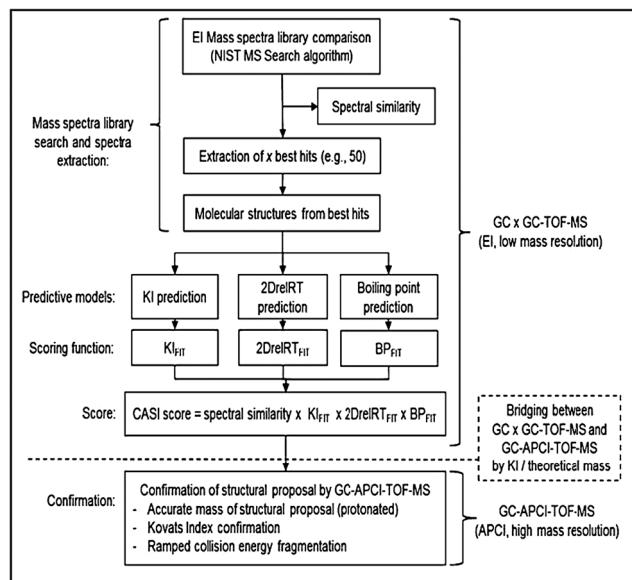


Fig. 10 The area of ethyl octanoate (36) and ethyl (*E*)-3-octenoate (37) elution depicted using GC × GC-TOFMS with GC-EAD analysis of the *C. capitata* male pheromone; extracted from ref. 198.

The combined analysis of GC × GC-TOFMS and GC-EAD was useful for the sex-specific analysis of antennal sensitivity in insects, such as determination of the female sex pheromone gland extract of the persimmon bark borer, (*Euzophera batangensis*),<sup>194</sup> as well as the male pheromone from medfly (*Ceratitis capitata*).<sup>195</sup> As shown in Fig. 10, GC-EAD analysis detected two distinct physiological responses corresponding to co-eluted ethyl octanoate and ethyl (*E*)-3-octenoate compounds, which can be depicted clearly in the GC × GC-TOFMS analyses. It is of interest to incorporate the MDGC approach into enantioselective separation GC-EAD, which reportedly plays an important role for identifying the reciprocal behavioural agonist–antagonist activities of enantiomeric pheromones,<sup>196</sup> and to confirm the natural supellapyrone enantiomer cockroach sex pheromone.<sup>197</sup>

#### MDGC strategy for unambiguous molecular analysis

When MS alone is insufficient to provide unambiguous measurement for either overlapped compounds, or where MS data are equivocal, unambiguous chemical identification requires a pure compound to be obtained, followed by structure elucidation using spectroscopic techniques, principally NMR spectroscopy and MS. A preparative technique based upon capillary column GC-GC with 1D and 2D NMR was proposed which is able to resolve, isolate, and identify pure volatile components from a complex sample.<sup>57–59</sup> 1,4-Dimethoxybenzene, and geraniol from an essential oil matrix, and 1- and 2-methylnaphthalene from a complex crude oil were successfully isolated and collected at up to 10s of µg level using this approach, with subsequent analysis by NMR spectroscopy. Recent applications of preparative MDGC coupled to isotope ratio MS<sup>199</sup> and Fourier transform infrared spectroscopy<sup>64</sup> have been reported, whilst studies on preparative GC with <sup>1</sup>H NMR and XRD<sup>200</sup> and bioassay methods<sup>201</sup> further demonstrates the potential of preparative MDGC for explicit molecular study. Chin *et al.*<sup>202</sup> reported an online solute enrichment approach using an internal cryogenic trap in the GC-GC system, which is a valuable adjunct for detectors of low sensitivity without compromising solute resolution.



**Fig. 11** General computer-assisted structure identification (CASI) conceptual process; extracted from ref. 159.

Monitoring of polycyclic aromatic sulfur heterocycles (PASH) in crude oil and coal tar samples was performed comprehensively using sequential heart-cut MDGC-MS/flame photometric detection after silica gel fractionation.<sup>203</sup> From the clean mass spectra of sample components acquired by GC-GC-MS, PASH components were identified according to combinatorial ion selection, multiple fragmentation patterns per homologue, and spectral deconvolution of homologue patterns with retention windows. A combinatorial library for PASH was built, and validated for measurement accuracy. Knorr *et al.*<sup>159</sup> proposed an automated platform for high throughput metabolite identification with GC × GC-TOFMS and GC-APCI-TOFMS techniques (referred to as computer-assisted structure identification, CASI) as illustrated in Fig. 11. Likewise, such an approach was based upon the proposed mass spectral library acquired by GC × GC separation followed by subsequent refinement using prediction models for separation and boiling point, and molecular structure confirmation by accurate mass.

## VI. Future directions

Application of MDGC with porous layer open-tubular (PLOT) column for analysis of gaseous and highly volatile compounds is scarce,<sup>204–208</sup> yet the impact would be significant for planetary and atmospheric studies. An automated GC system – Medusa – incorporating multiple cryogenic trapping devices was developed for *in situ* analysis of the anthropogenic emission of greenhouse gaseous including various halocarbons and nitrogen trifluoride ( $\text{NF}_3$ ) in trace amount.<sup>209,210</sup>  $\text{NF}_3$  was found to be separated from  $\text{CH}_4$  and Kr gases to a limited extent only when depicted by  $m/z$  52, 15 and 78 respectively in 1D GCMS analysis. Another *in situ* headspace sampling GC analyser suited to the analysis of volatile fragrance compounds was recently illustrated with the demand of higher resolving efficiency.<sup>211</sup> Most likely, emerging MDGC

approaches exploiting new stationary phases designed for specific applications will be increasingly described.

Tranchida *et al.*<sup>212</sup> regulated the flows in the GC × GC system using different degrees of flow splitting at the  $^2\text{D}$  column head pressure for greater resolution, since many GC × GC methods employ a non-optimum carrier flow velocity for the  $^2\text{D}$  column due to conventional method implementation. Peroni *et al.*<sup>213</sup> reported development of GC × multi-GC analysis with the use of three parallel capillary columns as  $^2\text{D}$  in an attempt to achieve simultaneous optimum-velocity operation. Whilst the presence of modifier in a SFC mobile phase dramatically improved retention and efficiency for polar solutes,<sup>214</sup> online reaction GCMS<sup>215</sup> offers an alternative for additional separation dimension through fine tuning in the GC mobile phase. Modification of the carrier gas thus exhibits a new challenge to push the limit of MDGC separation for thermally labile and polar analytes.

Recent study reported a retention projection methodology that enables 3-fold more reliable use of shared gas chromatographic retention data across laboratories, instruments, and methods.<sup>216</sup> Relevant database development is urged for the GC × GC method, since databases are usefully employed for 1D GC and GC-MS methods. To date, little has been reported for reducing the GC × GC method to a functional database comprising fixed retentions in the 2D space, correlated with identification of components. This is not surprising since there is little consensus on preferred column sets used for different applications, although certain columns are apparently more popular. Along with current developed structure elucidation algorithms,<sup>217–219</sup> this would allow highly accurate identification of unknown components through the retention information acquired from multiple separation dimensions of the MDGC analysis.

Whilst this review chooses to focus on the separation attributes arising from MDGC, and mass spectrometry deserves a separate coverage, brief commentary on MS for MDGC is warranted. Hyphenation of MDGC with various types of descriptive detection tools such as MS (e.g. qMS, TOFMS, HRMS, and IRMS), including different ionisation mechanisms, results in a powerful analytical tool that generates a wealth of informative data for complex sample analysis. Many of the above applications include a further dimension of MS identification. The MS-hyphenated technique and its role has been long recognised and is the subject of various reviews.<sup>31,121,220,221</sup> GC × GC has considerably more constraints upon the types of MS methods that can be used, specifically because of the fast chromatographic peak flux. For a peak about 0.2 ms wide, fast MS data acquisition is required. Maximum scan rates of the qMS is about  $10\ 000\text{--}20\ 000\ \text{Da s}^{-1}$ . Depending on the mass scan range, the qMS may scan at about 20–40 Hz. Operating the qMS in SIM mode will permit increased cycle rate, but only for a limited number of simultaneous ions. The qMS can be used with GC × GC, but the higher data rate of TOFMS makes this a preferred option, with 50–100 Hz commonly reported. This will give about 10–15 scans across a GC × GC peak. Little research has reported MS/MS modes of analysis,<sup>222</sup> primarily due to the need for speed of acquisition. By contrast, GC-GC peaks elute more slowly into the MS, and so now MS/MS modes are possible. Continued development of MS ionisation<sup>194,195</sup> such

as atmospheric-pressure photo-ionisation (APPI) or atmospheric-pressure laser ionisation (APLI) are outstandingly sensitive, and these provide a measure of selectivity toward specific chemical classes for moderately- to non-polar aromatic compounds.<sup>223,224</sup> Development of GC × GC-SPIMS<sup>116</sup> and GC × GC-QTOFMS<sup>225</sup> approaches have been studied recently. However, the on-going innovations in tandem MS with novel ion dissociation and labelling probes delivers comprehensive insight of gaseous molecules.<sup>226</sup> It is anticipated that direct coupling of such techniques with a pre-separation MDGC step, possibly with computational modelling and simulations, holds many advantages for precise analysis especially for complex biological samples.

## VII. Conclusion

Gas chromatography is widely used in chemistry and biochemistry for numerous tasks. High resolution MDGC has now become a filtering process that provides molecular size, structural orientation and functional group correlation. The advent of novel GC stationary phases that offer different selectivity, especially in the multi-dimensional separation experiment, is important for maximising orthogonality in a 2D experiment.

The suitability of the GC experiment for multiple separation dimensions, with multiple columns interfaced in a facile manner, a range of flow switching devices, storage loops, and especially with new cryo-trapping procedures that serve the process of both trapping and also act as rapid re-mobilisation of solute, permit an extensive array of new operational procedures in GC. These all have a single goal – to provide improved analysis of either global or target analytes. But new GC-GC and GC × GC procedures belie the information that can now be extracted, above and beyond just a simple separation system. Certainly, very complex samples can be better resolved, but by careful implementation, processes such as molecular interconversion phenomena can be studied in ways not possible in a 1D method. Also, a GC × GC method can provide details on the molecular heterogeneity of a sample through a chemical compositional map simply by choice of the column phases employed in <sup>1</sup>D and <sup>2</sup>D. Sample comparison is now much more information-rich, and chemometrics procedures are being developed to take advantage of this opportunity. Much greater separation – ideally with solutes completely resolved – suggests the use of spectroscopic detection in a prep-GC mode can support certainty of compound identification.

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