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Technical note: Why choose a time-of-flight mass spectrometer?

Modern labs must constantly adapt to cope with new analytical challenges and ever-increasing workloads, all while improving data confidence and reducing associated costs. This technical note highlights why time-of-flight mass spectrometry (TOF MS) is an ideal choice to address these challenges in both research and routine applications, by delivering fast, highly sensitive detection with full spectral information, for comprehensive sample characterisation in a single run.

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Introduction

Gas chromatography coupled with mass spectrometry (GC–MS) is a powerful tool for the separation and characterisation of volatile organic compounds (VOCs) in solid, liquid or gaseous samples.

The fundamental role of the mass spectrometer is to identify the individual analytes in the sample mixture. It does this by ionising molecules as they elute from the GC, separating the ions based on their mass-to-charge ratio (m/z) and creating a unique fragmentation pattern that is recorded as a mass spectrum. The mass spectrum can be interpreted to uncover the identity of the compound – though nowadays, this process is automated using extensive commercially available spectral libraries.

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While identification is the main purpose, mass spectrometers are also ideally placed to provide quantitative measurements of the analytes, making them one of the most versatile and important tools for the analytical chemist.

For this reason, GC–MS is widely used across a host of scientific fields, such as food authenticity studies, environmental monitoring and forensic analyses. However, there are so many commercial MS platforms to choose from that purchasing a new GC–MS can be a difficult and time-consuming decision.

In 1984, McLafferty proposed the criteria of six Ss for consideration when purchasing new analytical instrumentation that are still relevant:[1]

- **Sensitivity** – What detection limits are required for your application and are you confident you won't need to detect lower levels of additional compounds in the future?
- **Speed** – What is the acquisition speed of the MS, as well as the time taken for the full workflow, from sample preparation through to delivery of results?
- **Specificity** – How well can the system cope with complex mixtures? Typically, best results are achieved through a combination of high-performance GC and high-performance MS.
- **Simplicity** – How easy is it to produce high-quality results?
- **Sampling** – How is the sample (liquid, solid or gas) introduced to the instrument?
- **$** – What budget is available? Obviously, the capital cost is a major factor in purchasing decisions, but the running costs and instrument up-time that contribute towards the overall cost of getting results should also be considered.

In this technical note, we explore the advantages of TOF MS, specifically SepSolve's BenchTOF2™ instruments, in relation to these criteria, and demonstrate why it is an ideal choice for both research and routine applications.

What is TOF MS?

TOF MS is one of the simplest and most powerful forms of mass spectrometry and uses the principle that when different ions are supplied with a given energy, the heavier ions will take longer to travel the fixed distance from the ion source to the detector.

In TOF mass spectrometers, such as BenchTOF2 (illustrated in Figure 1), the time taken for ions to cover the fixed distance from the ion source to the detector (dotted red line) is directly proportional to their m/z value. This allows ions across the entire m/z range to be monitored in one run, making TOF instruments ideal for a range of challenging qualitative and quantitative applications.

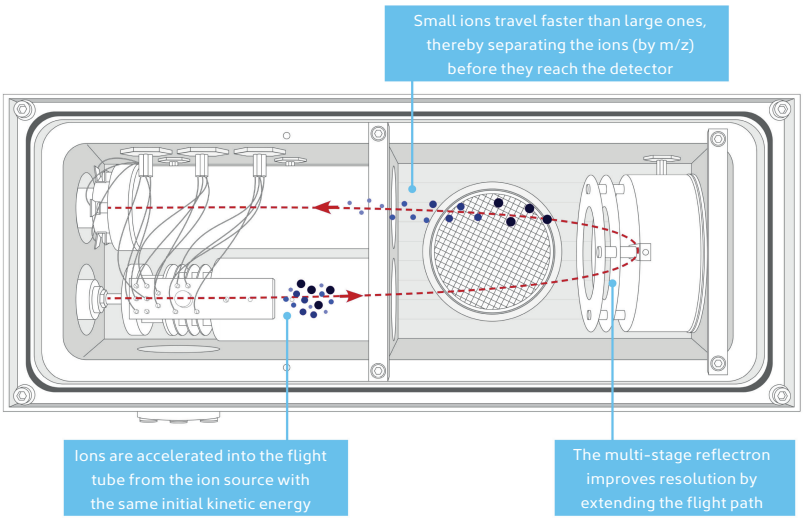

Figure 1

Schematic of the flight box in BenchTOF2 time-of-flight mass spectrometers.

In contrast to conventional quadrupole mass spectrometers, which work by mass filtering, TOF instruments simultaneously analyse all ions. This makes them far less wasteful, and so inherently more sensitive. Figure 2 provides a schematic of a single quadrupole MS, illustrating how these instruments scan through the mass range, with only ions of a specific mass-to-charge ratio reaching the detector at any one point in time, while all other ions are discarded.

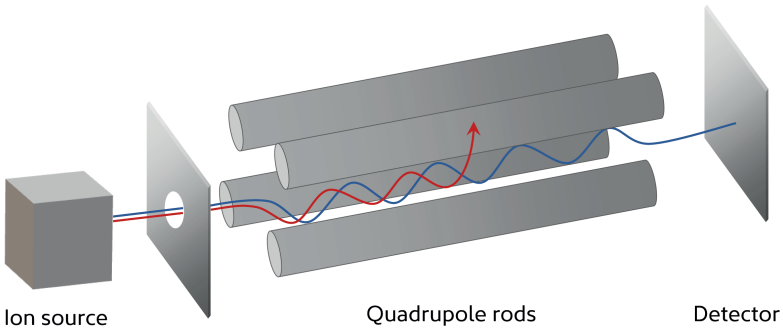

Figure 2

Simple schematic of a single quadrupole mass spectrometer. The blue line represents an ion selected to reach the detector, while the red dotted line represents an ion with a different m/z ratio that was discarded in this mass filtering approach.

Instrument	Targets	Non-targets	Sensitivity
Single quadrupole MS (scan mode)	✓	✓	×
Single quadrupole MS (SIM mode)	✓	×	✓
Time-of-flight MS	✓	✓	✓

Although the sensitivity of quadrupoles can be boosted by use of a selected ion monitoring (SIM) mode, in this mode only target compounds can be monitored, meaning that full characterisation of the sample is not possible in a single run, and retrospective searching of data is impossible. Therefore, there is always a compromise when using single quadrupole systems.

TOF mass spectrometers overcome this issue by providing highly sensitive detection whilst acquiring full-range mass spectra. The result is that they allow identification of trace-level targets and unknowns in a single, rapid analysis.

What are the key advantages of TOF MS?

Confident identification of targets and unknowns

Many applications of GC–MS now require a detailed understanding of the entire sample composition rather than simply focusing on a list of target compounds. For example, in food and fragrance analyses, non-target screening is applied to gain as much insight as possible into the odour-active compounds that will contribute to the overall perceived aroma.

Detection using TOF MS provides the sensitivity and data density needed to deconvolve the profiles of trace-level compounds in complex samples, such as the two esters shown in Figure 3, which were identified in hops. TOF MS instruments are well-suited to the application of deconvolution since they do not produce spectral skew across peaks. In quadrupole MS, due to the time it takes to scan across the m/z range, differences are seen in the spectra at the start, apex and end of the GC peaks, making it challenging to apply robust deconvolution.

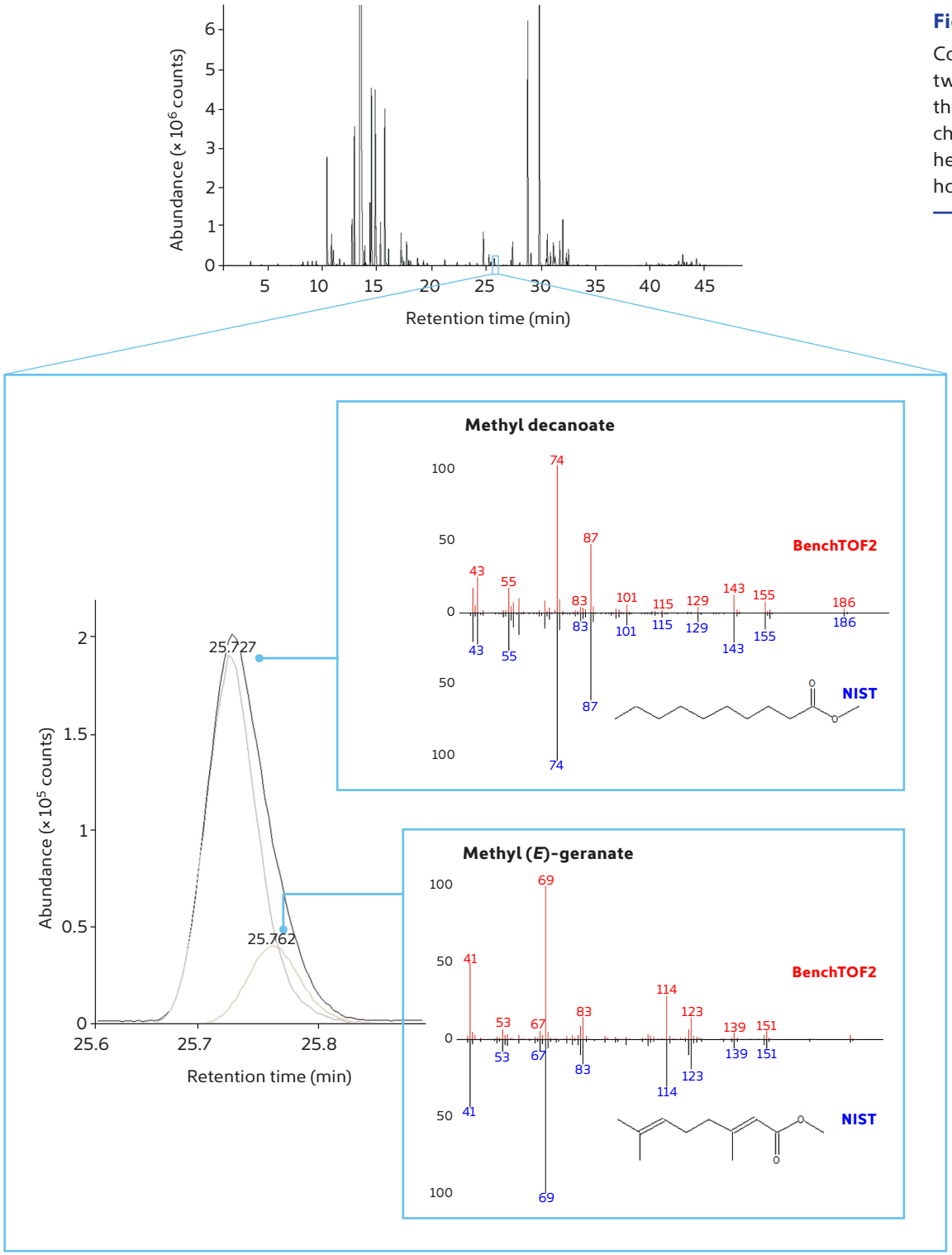

Figure 3

Confident identification of two co-eluting species in the GC–TOF MS chromatogram for the headspace volatiles from hops.

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It is also important to note that strong match factors (MF > 900) were obtained for both compounds in Figure 3, indicating high confidence in the identification. The NIST database of mass spectra comprises more than 90% quadrupole-originating spectra. Uniquely among TOF manufacturers, BenchTOF2 generates quadrupole-like spectra that do not suffer mass discrimination (undesirable skew). Other commercial TOFs suffer from mass discrimination, such that the ion intensities of larger m/z values are under-represented (Figure 4). BenchTOF2 instruments use advanced optics and an ion source floating at 3000 V to minimise differences in ion impact velocity at the detector. As a result, spectra closely match those in NIST and other commercial or legacy libraries, so there is no need to acquire new libraries of replicate spectra for high-confidence library searching.

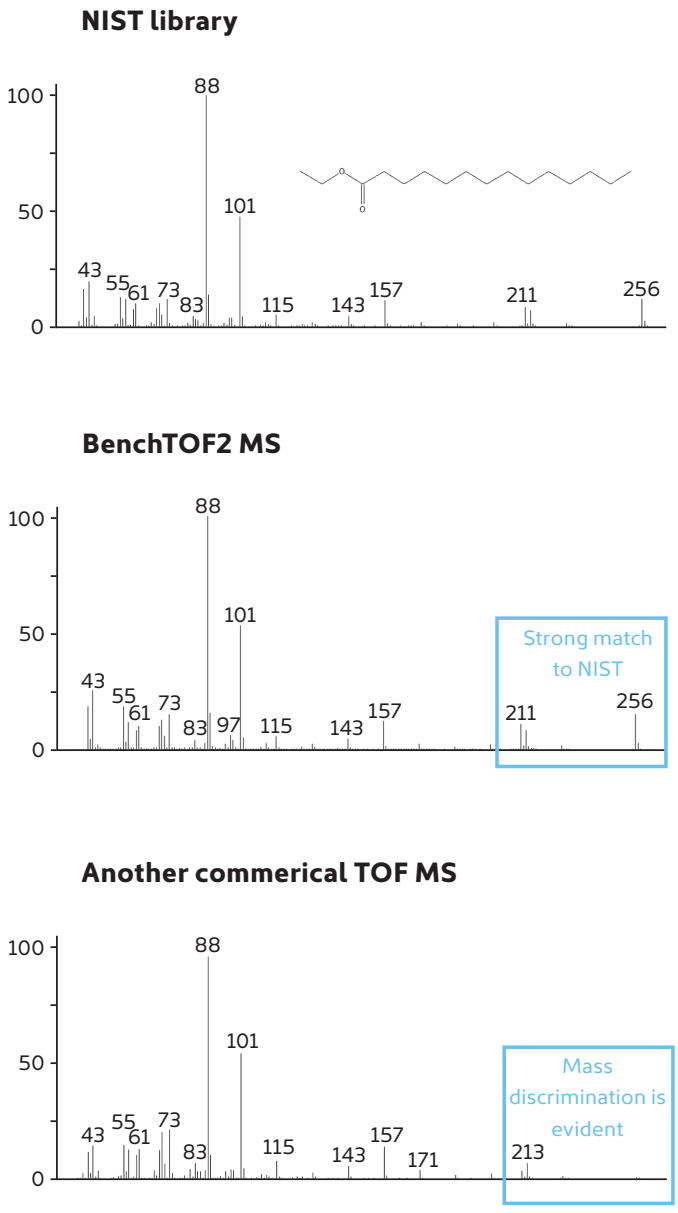

Figure 4

Comparison of the NIST entry for ethyl tetradecanoate with the spectra obtained by BenchTOF2 and another commercial TOF MS platform.

Improved productivity in quantitative applications

In recent years, there has been increased demand for systems offering improved sample throughput while maintaining or improving analytical performance. Typically, fast GC is employed, using fast oven temperature ramps and narrow-bore columns to achieve analysis times of under 10 minutes.

However, in such analyses, the resulting peaks are often in the range of 1–2 seconds wide, meaning that fast acquiring detectors are required to obtain enough datapoints to accurately define a peak (Figure 5). For quantitative purposes, it is generally accepted that 10–20 datapoints are required[2] – in other words, speeds of at least 10 Hz are needed to accurately define one-second-wide peaks.

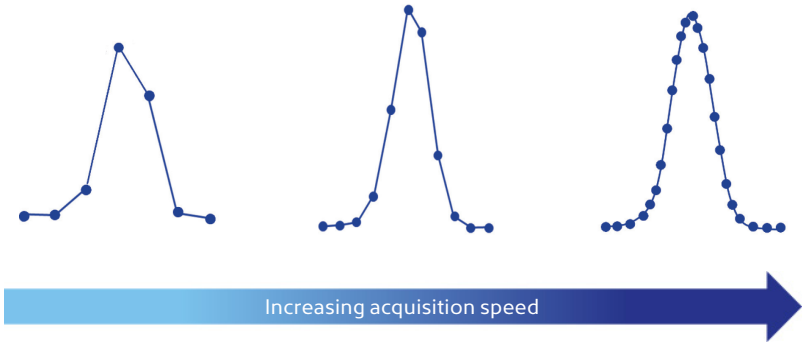

Figure 5

Illustration of how increasing acquisition speed can impact chromatographic peaks (note that the start/end points, apex and shape are all affected).

In Figure 6, a GC–TOF MS total ion chromatogram (TIC) is displayed for fast analysis of a contaminated soil sample, with an example calibration curve displayed for one of 16 priority polycyclic aromatic hydrocarbons, with excellent linearity over five orders of magnitude (from 500 fg to 100 ng).

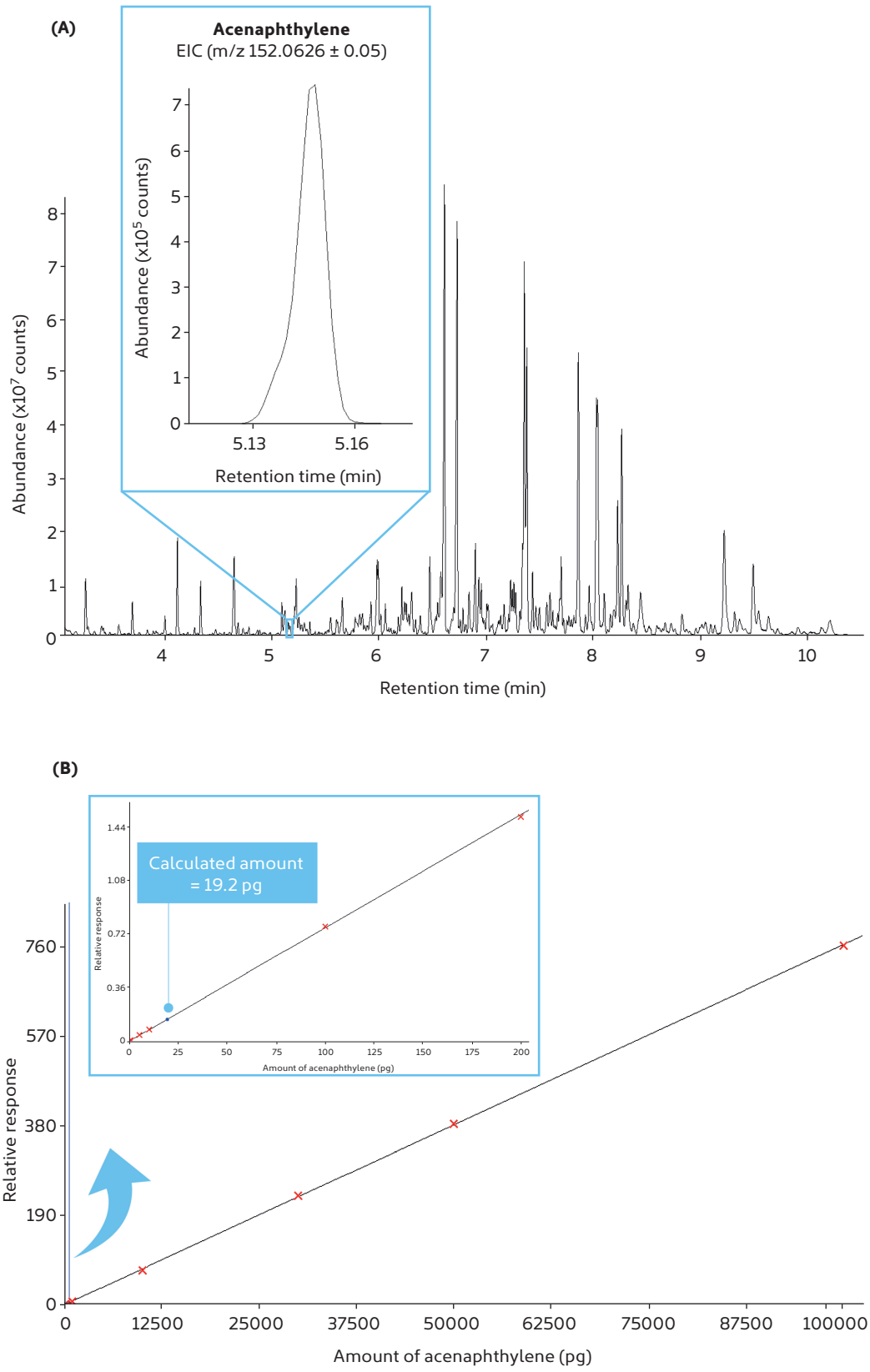

Figure 6

(A) GC–TOF MS chromatogram for a contaminated soil sample, with an extracted ion chromatogram (EIC) for acenaphthylene in the inset. (B) Calibration curve (from 50 fg to 100 ng) used to calculate the amount of acenaphthylene.

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TOF MS is inherently well-suited to handling such narrow GC peaks. This is because TOF mass spectrometers are dispersive (not scanning) instruments, and so effectively monitor all masses at once with fast acquisition rates.

Additionally, the fast acquisition speeds of TOF MS provide the opportunity to evolve capabilities and use advanced separations, such as comprehensive two-dimensional GC (or GC×GC). The rapid secondary separations in GC×GC frequently result in peak widths less than 100 ms, so detector speeds of 100 Hz are essential to maintain at least 10 datapoints across a peak (Figure 7).

The ability to record full-range mass spectral information to extremely high densities enables TOF MS to handle the narrowest peaks encountered in well-optimised GC×GC couplings. For example, in Figure 7, the enhanced separation of GC×GC–TOF MS is shown for a fragrance mixture, where many of the analytes would have co-eluted in one-dimensional GC analysis, but GC×GC results in sharp, well-separated peaks.

The expanded regions in Figure 7 clearly show that slow acquisition speeds of 10 Hz are unable to accurately define the GC×GC peaks, while 100 Hz provides improved chromatographic resolution (as highlighted by the arrows on the colour plot). BenchTOF2 is capable of acquisition speeds of up to 400 Hz to ensure that even the narrowest GC×GC peaks are accurately defined, for optimal qualitative and quantitative results.

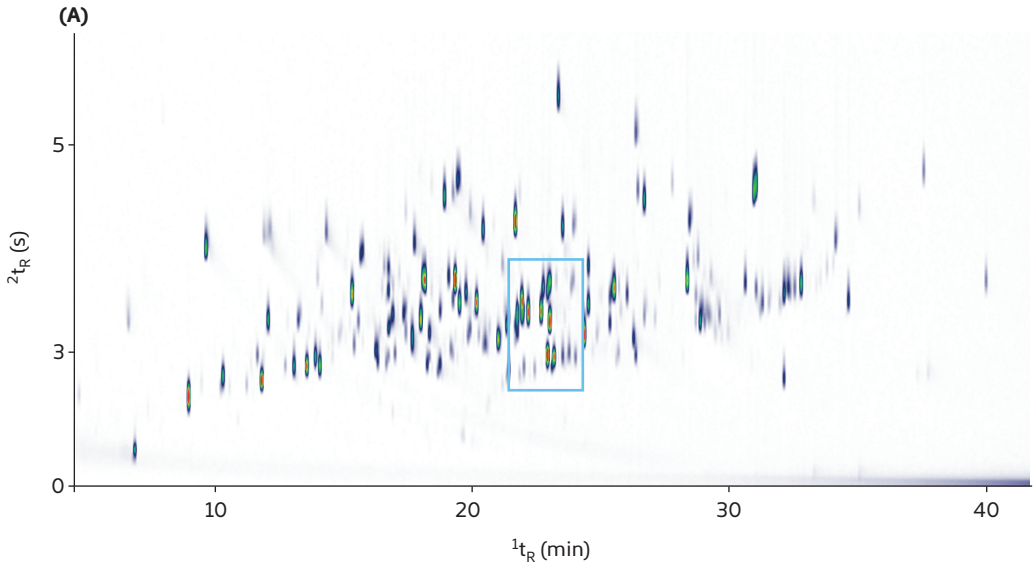

Figure 7

(A) Enhanced separation of GC×GC–TOF MS for a fragrance mixture, with expanded regions showing the comparison of (B) linear chromatograms and (C) colour plots generated using TOF MS acquisition speeds of 10 Hz and 100 Hz (*Continued on next page*).

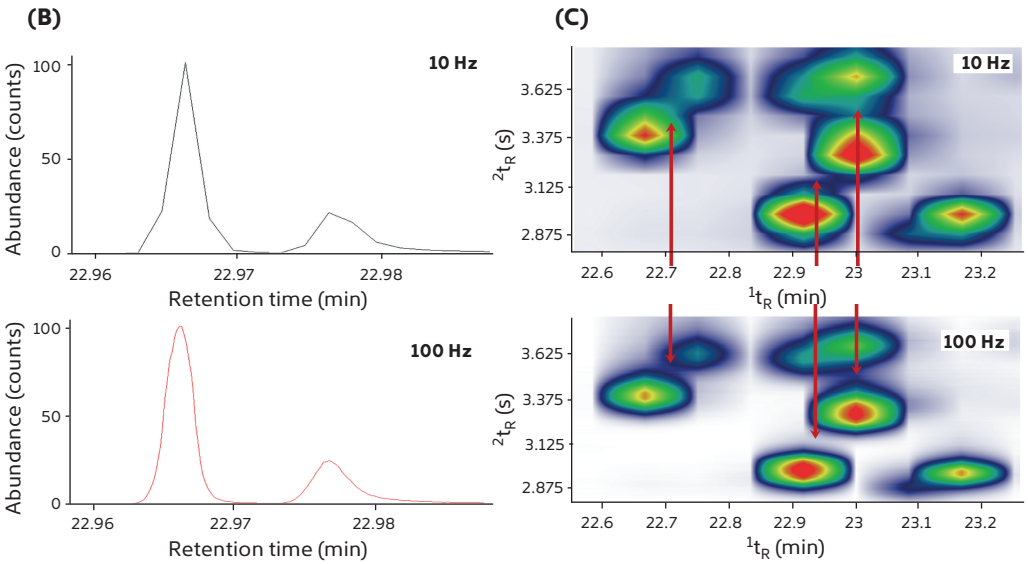

Figure 7

(A) Enhanced separation of GC×GC–TOF MS for a fragrance mixture, with expanded regions showing the comparison of (B) linear chromatograms and (C) colour plots generated using TOF MS acquisition speeds of 10 Hz and 100 Hz (*Continued from last page*).

Harnessing selectivity in simple workflows

Unlike quadrupole MS, TOF MS instruments are not typically restricted to nominal mass. Precise identification of target compounds becomes possible when sub-unit mass selectivity is used to eliminate matrix interferences. Signal-to-noise ratios are also improved when narrow-span EICs are used (as shown in Figure 4), enhancing quantitation of trace-level analytes in complex matrices. Figure 8 shows how the enhanced selectivity of BenchTOF2 instruments can be harnessed in easy-to-use workflows with the mass-to-formula calculator and isotope overlays in ChromSpace® software.

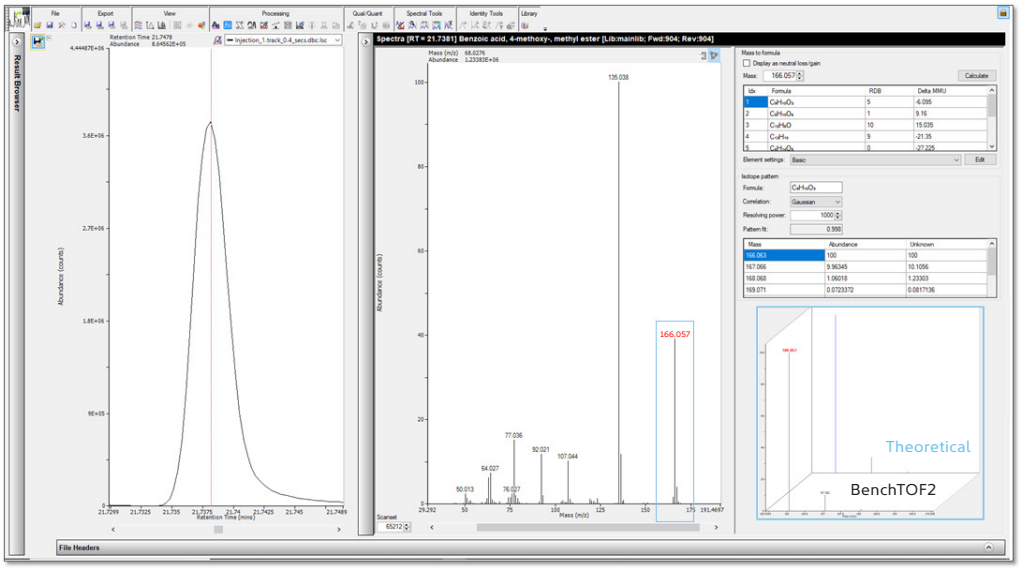

Figure 8

Confident compound identification using sub-unit selectivity of BenchTOF2 combined with smart software tools, such as the mass-to-formula calculator (top right) and isotope overlays (bottom right).

Not only can the isotope overlays be used to confirm compound identity, they can also be used to quickly find related compounds (Figure 9). In this case, thermal desorption (TD) was coupled with GC–TOF MS for confident and secure sampling of harmful compounds in air at a biological waste processing plant. The Compound Explorer toolkit in ChromSpace was then used for fast filtering of the complex chromatogram to reveal only the target compounds of interest. Here, only peaks exhibiting the unique isotope pattern of chlorine are shown in the filtered image.

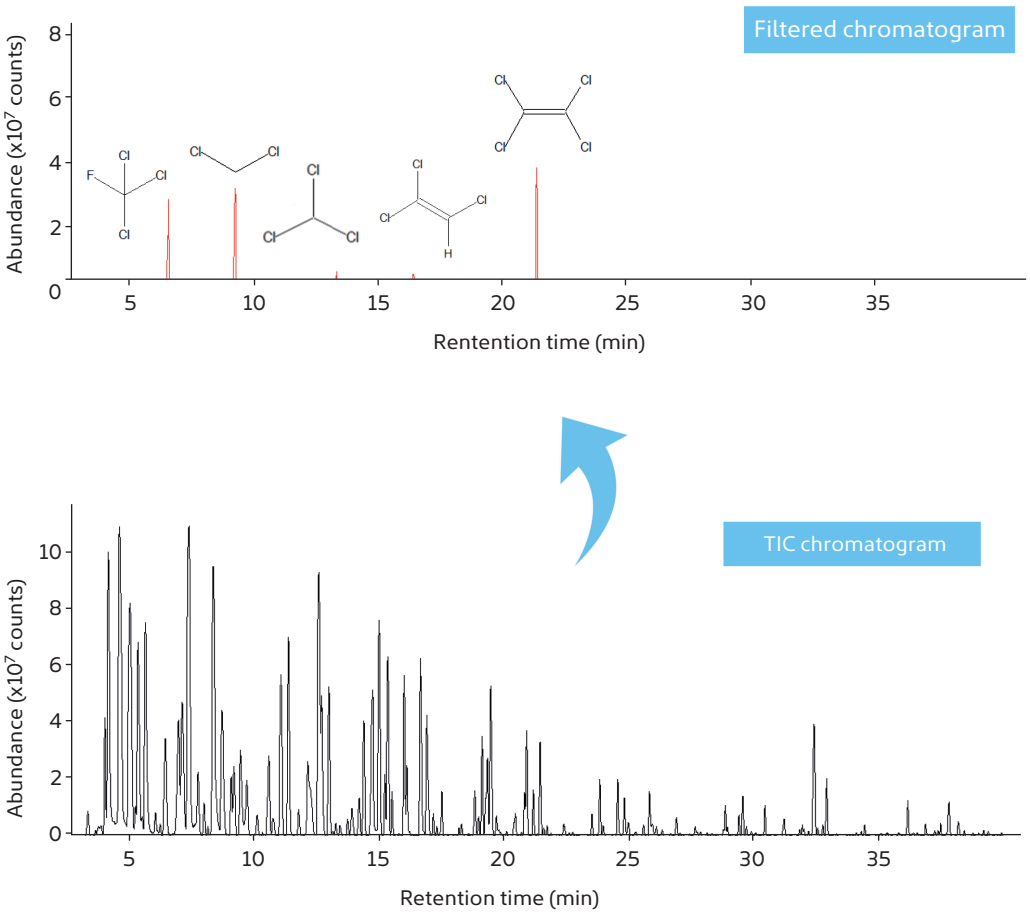

Figure 9

Thermal desorption (TD) coupled with GC–TOF MS for analysis of contaminated air, with simple filtering using the Compound Explorer toolkit to automatically reveal the chlorinated compounds present.

Addressing the isomer challenge

Using conventional 70 eV ionisation, many isomers (such as terpenes and branched hydrocarbons) share similar spectra, containing the same ions in slightly different ratios, making it impossible to identify the individual isomers confidently. Tandem Ionisation® for BenchTOF instruments solves this challenge by generating both 70 eV and soft EI ionisation spectra in a single acquisition. The technique uses fast switching (or multiplexing) between two ionisations, enabling two sets of spectra to be acquired at the same time – for dual library searching of reference-quality 70 eV spectra and soft ionisation spectra with stronger molecular ions and less fragmentation to improve discrimination between structurally similar isomers (Figure 10).

Find out more about what Tandem Ionisation can offer in our technical note: Tandem Ionisation® – Revolutionary soft ionisation to enhance confidence in identification.

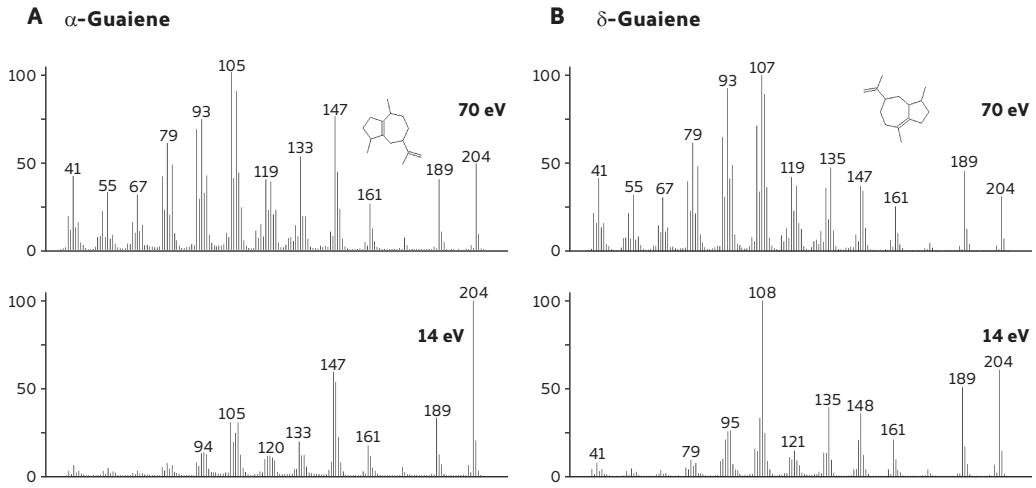

Figure 10

Comparison of the 70 eV and 14 eV spectra obtained for two isomers of guaiene, showing the enhanced differences in ion ratios obtained when using soft EI, for improved isomer speciation.

Minimal maintenance, maximum up-time

Finally, the instrument up-time is an important consideration, as this impacts ease of operation as well as productivity and the overall cost of obtaining results. In BenchTOF2 mass spectrometers, packets of ions are axially extracted from the ion source and are sent directly into the analyser. This is achieved with a very powerful pulsed electric field (3300 V) compared with the oaTOF geometry (oa = orthogonal acceleration) and quadrupoles, which use a continuous ion source (i.e., continuous ion beam) and an ion repeller with a relatively small field (1–30 V) to eject ions from the source. The use of axial extraction in BenchTOF2 results in long-term stability, obviating any additional source maintenance above and beyond annual preventative maintenance, thereby minimising downtime and improving productivity.

Conclusions

This technical note has demonstrated the advantages of using TOF MS – of which SepSolve's BenchTOF2 is a prime example – across a range of applications.

- Unlike quadrupole mass spectrometers, TOF MS instruments monitor all masses at once, making them ideal for high-sensitivity detection of targets and unknowns in a single run.
- High data density and elimination of spectral skew provide optimal results for deconvolution, to ensure that co-eluting compounds are not overlooked.
- TOF MS instruments provide enhanced selectivity to eliminate interferences and improve detection of trace compounds in complex matrices.
- The fast acquisition speeds of TOF MS instruments are well-suited to fast, quantitative GC and GC×GC applications for improved separation of complex samples.
- The need for cleaning or maintenance is greatly reduced, maximising up-time and improving productivity.

References

[1] F.W. McLafferty, Trends in analytical instrumentation, *Science*, 1984, 226: 251–253.

[2] R.C. Blase, K. Llera, A. Luspay-Kuti and M. Libardoni, The importance of detector acquisition rate in comprehensive two-dimensional gas chromatography GC×GC), *Separation Science and Technology*, 2014, 49: 847–853.

Applications were performed under the stated analytical conditions. Operation under different conditions, or with incompatible sample matrices, may impact the performance shown.

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