Introduction to ToC-MS™

The ToC-MS Concept

Prof Peter O'Connor's team at the University of Warwick, has developed an innovative technique called Total Correlation Mass Spectrometry™ (ToC-MS). ToC-MS allows fragmentation of a wide range of molecules and maintains a correlation between each fragment and its precursor. This correlation is automatic and facilitates rapid data analysis of complex samples.

The technology was developed on an FTICR, but the technique is now available on routine, benchtop mass spectrometers that are fast enough to provide comprehensive fragmentation datasets in a few seconds.

Even when a sample contains thousands of precursors; the ToC-MS approach can acquire fragmentation data for all precursors simultaneously; automatically correlating every precursor with all its fragment ions.

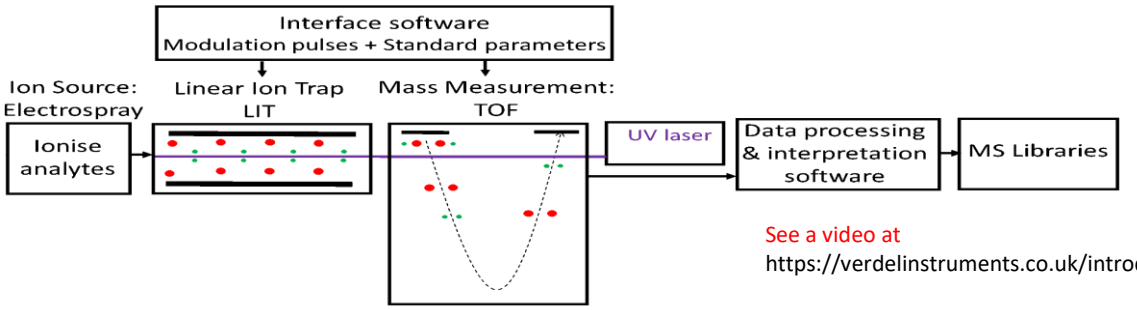
ToC-MS means that true data independent acquisition can finally be bought into mainstream use by the MS community.

The Instrument

The technique exploits the fact that the position of the ions in a linear ion trap (LIT) can be modulated, and that the fragment ions will always have the same frequency as the precursor ions.

The modulation technique used to control the position of the analyte ions in the LIT is called Stored Waveform Ion radius Modulation (SWIM) and it uses radiofrequency voltages that are applied to the electrodes of the LIT to manipulate the positions of the ions.

A UV laser is used for fragmentation, which is both efficient (e.g. capable of cleaving peptides and proteins at nearly every amino acid) and high speed (i.e. fragmentation in 1 nanosecond). Precursor Ions at the centre of the LIT are fragmented with a much higher efficiency than precursor ions at the edge of the LIT, which means that fragment ions are always modulated in the same way as the originating precursor ion.



See a video at
https://verdelinstruments.co.uk/introduction-to-ToC-MS

After fragmentation, all the ions in the LIT (unfragmented precursor ions and fragment ions) travel through the TOF where their m/z ratios and abundances are measured.

During data processing, the modulation frequencies of the abundance at each m/z ratio are calculated. The Fourier transform then relates each fragment ion to its respective precursor analyte ion, providing structural information on all the analytes in the sample without missing the lower abundant analytes.

The data can be plotted as a ToC mass spectrum and converted into files that can be submitted to mass spectrometry libraries.

Users can optimise their analysis by specifying the parameters for the modulation pulses that are applied to the electrodes of the LIT for ToC-MS.

The interface also records and stores the raw data from the mass measurements in the TOF.

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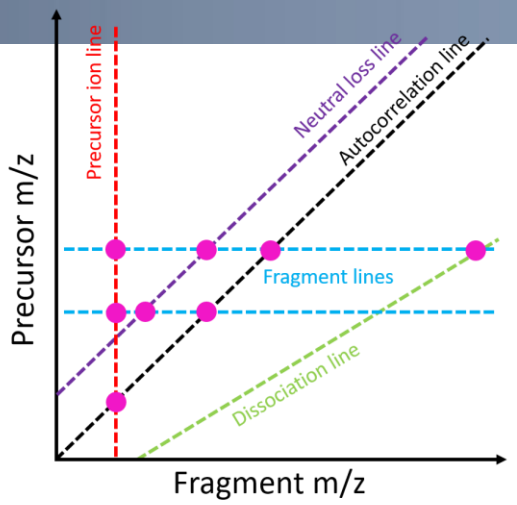
ToC-MS Spectra

ToC mass spectra contain not just the mass spectrum of the analytes from the sample (shown by the autocorrelation line on the figure) like a traditional mass spectrum, but also the fragmentation pattern of every precursor ion (the fragment ion scan), the precursor pattern of every fragment ion (the precursor ion scan), and neutral loss and dissociation lines that can be used to find classes of ions in the sample that fragment in identical ways – indicative of similar structures (protein forms with different post-translational modifications, for example).



Applications

Some key applications for ToC-MS are;

- With samples that contain multiple analytes (the more complex the sample, the greater the advantage).
- With complex samples matrices containing many contaminants.
- When there are too many analytes to isolate in the timeframe available.
- When analytes are difficult to isolate.
- When the analytes have similar structural moieties.
- With chromatography where retention times drift.
- Where the user needs a reduction in run time to increase throughput.

The Benefits

Using ToC-MS for intrinsic correlation of precursor ions and fragments has the following benefits:

- Speed of analysis – complex samples with co-eluting peaks can be run at the speed of the Q-TOF.
- All sample data are acquired as every precursor is fragmented.
- Unambiguous, automatic correlation of precursor ions and their fragments, irrespective of how many analytes are in the sample.
- The method is highly reproducible because of the absolute correlation of precursors and fragments.
- Because this is a true data independent acquisition technique, all data acquired is objective. No bias or variability is introduced by the use of sampling bins.
- Data acquisition is not limited by quadrupole isolation performance.
- The technique can overcome issues caused by chimeric spectra.
- The use of the 2 dimensions combined with Fourier transform can significantly increase the sensitivity of the instrument, with resolution down to mDa.
- A true DIA approach means that all possible data can be acquired from each sample, facilitating retrospective data analysis.
- Compatible with a wide range of solvents.

The Future

In the longer term, users will have access to application specific software for applications such as bottom-up proteomics, metabolomics, lipidomics, small molecules, top-down proteomics, polysaccharides, and polymers.

There will also be interpretation software for hydrogen-deuterium exchange analysis (3D structure of analyte through the measurement of how fast hydrogens can be replaced by deuterium).

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