Orbitrap™: Ten Years Young

Coupling gas chromatography with Orbitrap™ technology wasn't easy, but the outcome – the introduction of the Thermo Scientific Q Exactive™ GC – represents a big step towards bringing full-scan, high-resolution, and accurate mass data into routine labs around the world. And my dream of an "Orbitrap in every lab" inches ever closer.

By Alexander Makarov, Director, Global Research Life Science Mass Spectrometry, Thermo Fisher Scientific, Germany.

We started thinking about GC Orbitrap technology a long time ago – very soon after the dust had settled following the launch of the first commercial instrument at the June 2005 ASMS Conference in San Antonio, Texas – the LTQ Orbitrap tandem mass spectrometer. But back then it was clear that one or two second peaks were too narrow for the wide application of Orbitrap technology in GC. Nevertheless, Joshua Coon (a professor at the University of Wisconsin-Madison) expressed an interest and we initiated a research project to look at the potential. Originally, the project was simply a continuation of the mainstream work in his lab, which focused on electron transfer dissociation (ETD) for the LTQ Orbitrap instrument. At that time, ETD utilized anions that essentially came from the ion source of a GC quadrupole system, and so the connection was relatively straightforward. Indeed, the work resulted in the first rudimentary GC Orbitrap system. The initial data proved that there was high potential, but also indicated some challenges.

Amelia Peterson (from the Coon Research Group) came to the Thermo Scientific research lab in Bremen, Germany to continue work on the GC-MS-LTQ Orbitrap instrument and, on her return to UW-Madison, presented several applications in high-impact journals. Although the projects were only exploratory in nature, they proved invaluable in allowing us to gauge interest in GC-Orbitrap technology – and a number of customers began asking for more information.

An essential confluence

In reality, we were not able to communicate any fixed date about GC Orbitrap technology to our customers. We needed to fully assess what was needed in the market and put together an entire development team – and Orbitrap technology was still not ready for GC.

Over the next few years, information was gathered and the potential became clearer – but, more importantly, Orbitrap technology development continued. By 2011, we had increased the speed of the Orbitrap by a factor of four, by combining two innovations: i) enhanced Fourier transform algorithms, which doubled resolving power, and ii) the high-field "compact Orbitrap" (where an increase from 3.5 kV to 5 kV boosted frequency by 20 percent and the smaller trap provided a factor of 1.8 increase in speed.) Finally, we had an Orbitrap analyzer that was completely compatible with GC separations. At the same time, a talented development team became available in Austin, Texas, which could take on the not insignificant challenge of giving GC its first new mass analyzer in half a century.

Without these streams coming together, we could not have moved forward; the confluence of user demand, increased Orbitrap capability (in terms of speed, sensitivity, mass accuracy and selectivity), and the necessary resources gave us the critical mass we needed to begin in earnest. At which point, the ball started rolling very quickly.

What Orbitrap technology means for GC – and vice versa

At ASMS 2015, exactly 10 years after the introduction of the LTQ Orbitrap system, we launched the Q Exactive GC – an excellent way to celebrate Orbitrap's anniversary. What does Q Exactive GC offer the world of GC-MS? The real breakthrough is the combination of accurate mass with high sensitivity. Imagine a triangle of mass accuracy, sensitivity and speed – traditionally, optimization of mass accuracy comes at the sacrifice of the other two factors. Instruments that were not constrained by mass accuracy – triple quadrupoles, for example – were far ahead of the game in terms of sensitivity and speed. On the other hand, the only accurate mass instruments – time-of-flight systems – suffered from a severe compromise in other features. In other words, the size of the triangle is limiting. Orbitrap technology expands the triangle so drastically that we can now match the speed and sensitivity of triple quadrupoles, but at the same time provides high mass accuracy and resolution.

Since its launch, I've been pleased to see an extremely enthusiastic reception to the Q Exactive GC from the community. People are excited to learn how their

samples behave; we've already shared stories from Hans Mol in pesticide analysis, Karl Burgess in metabolomics, and Jana Hajšlová in food authentication in this article series – and I think there will be many more interesting stories to be told as the technology is adopted in labs around the world.

GC is an interesting addition to Orbitrap technology as it combines high resolution GC separation (with its large peak capacity) with the high resolving power (and mass accuracy) of the Orbitrap mass analyzer. The combination allows us to look deeper into the volatile and semi-volatile end of the analytical spectrum than we have done before – and with high clarity. Moreover, classical GC-MS with electron ionization reduces the need for MS/MS analyses, making straightforward full scan a routine mode of operation, without losing vital fragment information.

Indeed, we were surprised how far simple full-scan MS analysis could take us, using a combination of spectral library matching (with the vast, commercially available nominal mass libraries) and high resolution-accurate mass filtering. Acquisition using MS/MS is still important, but is typically used with chemical ionization mode in the search for further structural information about a compound for higher level confirmation – or, of course, to help us build an understanding of a compound that is not known and does not appear in libraries. The point is that, even though the technology appears to be more complex, the high resolution and accurate mass gained actually make analyses simpler, reducing the need for tedious method development. I think that has surprised a number of experienced analysts.

Clearly, Orbitrap brings something very new to GC – but the innovation also means that our technology is stepping outside its more traditional setting in life science applications. For me personally that means a lot, because I believe that the combination of easy mass accuracy and sensitivity could benefit many other types of analysis – we just need to look further into where unique advantages can be gained.

We also learned a lot in the development process, for example, how to reduce or completely eliminate ion molecule reactions, which were not present in electrospray produced ions, but were visible for ions produced by electron impact ionization. And we have now adopted a modular approach – the Orbitrap is one module that can be combined with a number of different front-end modules (ion sources). And excitingly, we now have two product development lines – one for LC and one for GC. Though the Q Exactive GC is an important milestone in Orbitrap history, rather than considering that it completes the story, I like to believe that it is the beginning, with more expansion ahead.

Orbitrap trajectory

I can foresee several different trajectories for Orbitrap technology; for example, analysis of aerosols and other ion sources. And we have even discussed the potential of sending Orbitrap technology into space with various agencies – Orbitrap in orbit! Certainly, we are keen to investigate any area where the combination of analytical qualities that Orbitrap technology provides can add real value – and that takes time. But where serious opportunities exist, we will be pushing the boundaries of what is possible.

I would consider Orbitrap game-changing or even disruptive technology – especially now that we've entered into the world of GC with the Q Exactive GC – but I don't think all other MS technology will (or should) retire just yet. If we look back at the history of mass spectrometry, even some of the earliest examples of hyphenated analyzers, such as magnetic sector instruments, are still leading in those areas where they confer a distinct advantage – and there are probably more magnetic sector instruments produced today than 30 years ago. Yes, we will see expansion and contraction of market share, but each will retain its own niche – and it really depends how attractive those niches are. Certainly, LC and GC applications are growing rapidly, with thousands of instruments worldwide, so this area often gets all the limelight – and here I expect Orbitrap technology to continue expanding at a higher rate than other analyzers. Why? Because it is fundamentally simple technology; it uses three electrodes with one voltage and its data system is a conventional PC. As a result, it has the potential to be competitive to quadrupole instruments in terms of investment.

We're not quite there yet – after all, we are working at the edge of what humanity can provide in terms of electrode accuracy and electronics stability – but the simplification trend has already begun; for example, if you consider the evolution from LTQ Orbitrap with five turbomolecular pumps to Q Exactive with two, you can see the tendency to use acquired knowledge and advances to decrease complexity and increase accessibility. Another example is the introduction of the Q Exactive Focus – specifically for heavy workloads in environmental and food safety – at a price that is comparable with high-end triple quadrupoles. In other words, Orbitrap is on a continually shifting pathway – and I hope that will continue for years to come.

In the end, the simplicity of the Orbitrap analyzer's design will be key to the future simplification of the technology – at that point, my dream of an "Orbitrap in every lab" starts to sound realistic.

Video interview with Alexander Makarov: tas.txp.to/1015/MakarovGC
To find out more: thermoscientific.com/QExactiveGC