Ion traps in modern mass spectrometry

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Biographies

Dirk Nolting studied Chemistry at the Heinrich-Heine University Düsseldorf. His PhD thesis focused on photodissociation of electronically excited states of protonated molecules. Before joining Thermo Fisher Scientific he worked as Postdoc at the Max Born Institute for Nonlinear Optics and Short Pulse Spectroscopy investigating lifetimes and energy shifts of electronic states of protonated molecules. He currently works as a project manager and scientist on the further improvement of Orbitrap-based instruments at Thermo Fisher Scientific.

Robert Malek studied physics at Bremen University. His PhD thesis focus was devoted to FT-ICR mass spectrometry. At Thermo Fisher Scientific he was scientific lead developer for the LTQ FT mass spectrometer. His current focus is on intellectual property and data processing methods.

Alexander Makarov received his MSc and PhD in Moscow Engineering Physics institute. In 1996 he joined a small company, HD Technologies in Manchester (UK), where he started his work on the Orbitrap mass analyzer that later led to the commercial launch of LTQ Orbitrap mass spectrometer in 2005 and subsequent numerous extensions of this technology. He has received awards from ASMS, HUPO, IMSF, RSMS, Merck, etc. He holds the position of a Director of Research, Life Science Mass Spectrometry in Bremen, Germany and a Chair in High Resolution Mass Spectrometry at Utrecht University in The Netherlands. He has authored or co-authored more than 80 papers and more than 80 families of patents and patent applications.

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Abstract

This review focuses on trapping mass spectrometry wherein ions are confined by electromagnetic fields for prolonged periods of time within limited volume, with mass measurement taking place within the same volume. Three major types of trapping mass spectrometers are discussed, specifically radiofrequency ion trap, Fourier transform ion cyclotron resonance and Orbitrap. While these three branches are intricately interwoven with each other over their recent history, they also differ greatly in their fundamentals, roots and historical origin. This diversity is reflected also in the difference of viewpoints from which each of these directions is addressed in this review. Following the theme of the issue, we focus on developments mainly associated with the country of Germany but, at the same time, we make use of this review to illustrate the rapidly increasing globalization of science and expanding multi-national collaborations.

1. Introduction

This review brings together all three major directions of trapping mass spectrometry (MS), specifically its radiofrequency (RF) ion trap, Fourier transform ion cyclotron resonance (FT ICR) and Orbitrap branches. The main unifying theme of trapping MS is the confinement of ions by electromagnetic fields for prolonged periods of time within limited volume, with mass measurement taking place within the same volume.

While these three branches are intricately interwoven with each other over their recent history, they also differ greatly in their fundamentals, roots and historical origin. This diversity is reflected also in the difference of viewpoints from which each of these directions is addressed in this review.

Following the theme of the issue, we focus on developments mainly associated with the country of Germany but, at the same time, we make use of this review to illustrate the rapidly increasing globalization of science and expanding multi-national collaborations.

We start from presenting the earliest of the three techniques, RF ion trap, invented in Germany by W. Paul (this chapter is written by D. Nolting), followed by later inventions, FT-ICR and Orbitrap techniques, that were invented in other countries (FT-ICR in North America, the Orbitrap analyzer in the UK and in Russia) but prospered profoundly on German soil (these chapters are written by R. Malek and A. Makarov, respectively). As this review is dedicated to instrumentation development, it appeared to be possible to cover analytical applications only for the FT-ICR technique simply because of the smaller number of instruments, while the other two techniques are represented with such a massive multitude of instruments, groups and citations, that we attempted to only illustrate selected major fields of their use.

It should be noted that by focusing on trapping MS, this review necessarily excludes other large and very important applications of ion trapping. Such applications include, for example, quantum computing, accelerators, high-energy storage rings utilizing magnetic [Wolf, 1999] and/or electric confinement (e.g. CSR [Zajfman, 2005]) or instruments designed for the use with nuclear physics installations (such as SHIPTRAP , TRIGA-TRAP, HITRAP and others [Blaum, 2013]). This decision was not taken lightly but rather reflects the intention not to venture outside of the realm of analytical instrumentation represented by this journal.

An entire class of closed and open electrostatic traps with secondary emission detection of ion pulses [Makarov, 2010], otherwise known as multi-reflection time-of-flight (TOF) MS, was also considered to fall outside of the scope of this review because the detection method makes these instruments rather a part of the TOF-MS realm. However, similar traps with image current detection or resonant excitation are covered in Section 4.4.

2. Developments of radiofrequency ion traps

The interest in the use of alternating gradient quadrupoles for manipulating ion beams originated from molecular beam and particle accelerator physics [Paul, 1990]. In the early 1950's the research group of Wolfgang Paul at the University of Bonn worked on the development of new elements for manipulating and focusing particle beams. This also led to questions on the mass dependency of the trajectories of ions in devices such as magnetic and electrical quadrupoles. Theoretical considerations resulted in the prediction of a novel type of mass spectrometers where an ion can only reach the detector if the operating conditions are within specific regions. In 1953, Paul at al. proposed the use of hyperbolic rods in combination with electrical RF fields as a mass filter for charged particles [Paul, 1953] .

In the special case of hyperbolic electrodes the motion of ions can be described by the Mathieu equation. The solution of the Mathieu equation leads to the well-known stability diagram with parameters a and q describing the necessary working conditions for confining an ion in a quadrupole field [March, 1997]. The solution of the equation of motion for ions inside mass filters and ion traps reveal that ions oscillate at secular frequencies which are superimposed by the main RF frequency and depend on the conditions of the device and the m/z ratio of the ion. Thus, each ionic species oscillates at a different frequency. Ions can be resonantly excited by superimposing a weak (usually dipolar) electric field oscillating with the secular frequency. When in resonance, ions pick up energy at the secular frequency, gain amplitude and leave the trapping region. This is one of the main characteristics of RF ion traps and mass filters and has been exploited in several different modes of operation [Paul, 1958b].

The first experimental proof of this concept was presented two years later by Paul and Raether [Paul, 1955]. They used round rods with 10 mm diameter to record the mass spectrum of rubidium. The first RF mass filter achieved a resolution of 250. Later, Paul and co-workers were able to increase the resolution of their quadrupole mass filter to 1500. In one of the first experiments Paul and co-workers evaluated the use of the mass filter for isotope separation but the achievable transmission at the required resolution was rather low. The performance could be improved by reducing the resolution and removing unwanted isotope masses by resonant ejection[Paul, 1958b].

The logical continuation of the mass filter was the extension into a three-dimensional trapping field. The first mass spectrum which was recorded in an RF ion trap was published by Paul and co-workers [Paul, 1958a]. They presented the mass spectrum of krypton and could reach a resolution of 30 which was later improved to 85 by Fisher [Fischer, 1959]. Krypton ions were generated inside the ion trap by leaking Kr gas into the trapping region and guiding an electron beam through holes in one of the end caps. For detection the ions were resonantly excited by an auxiliary RF voltage between the end caps. The energy absorption in the excitation circuit was measured as a function of the AC and DC amplitudes of the main RF field [Fischer, 1959].

Nearly at the same time Wuerker with colleagues developed a 3D ion trap which allowed the optical detection of charged microparticles [Wuerker, 1959]. Schlemmer et al. replaced the ring electrode by eight rods for an improved access to the trapping region. With this set-up it was possible to investigate single nanoparticles (SiO_2, diameter 500 nm) by light scattering. The oscillations of the nanoparticle modulated the scattered light of a laser diode and the frequencies of the oscillation could be matched to the theoretically predicted secular frequencies. This

method is nondestructive. Therefore, the measurement could be repeated many times with different charge states created via electron bombardment. In this way, it was possible to determine the absolute number of charges of the particle. The absolute mass of the nanoparticle was measured with accuracy in the lower ppm range [Schlemmer, 2001; Schlemmer, 2004]. In another approach the ring electrode was replaced by a split ring electrode. C_{60}^{+} ions were heated with a CO_2 laser reaching stationary high temperatures in the range of 2000 K. The temperature was determined by blackbody radiation. This setup allowed the authors to measure decay rates below 1 / min [Gerlich, 2013].

The detection scheme used by Paul et al. was based on image currents and therefore pioneered this nondestructive method of detection. A different approach which is nowadays more common for commercially available ion traps detects the ions directly. Dawson et al. set up the confinement field such that only a small m/z range was trapped. The trapped ions were pulsed through one of the end caps and collected by an external detector. This reduced the complexity of the electronics and greatly improved the sensitivity but each mass required a separate scan cycle [Dawson, 1968].
The restriction that all trapped ions were ejected simultaneously was overcome by the mass-selective instability mode developed by G. Stafford [Stafford, 1984]. In this mode of operation the RF amplitude is slowly scanned after the ion trap is filled. Increasing the RF amplitude increases the lower mass cutoff, i.e., the stored ions become unstable in order of increasing m/z values. Ions leave the ion trap through holes in the end cap and strike a detector outside the trapping volume. The detector signal is measured as function of the RF amplitude which correlates directly with the m/z value of the detected particle.

The limited expansion of electrodes in real-world ion traps adds a weak negative octopole component to the trapping field. This causes a decrease of the secular frequencies with increasing distance from the center of the trap. An ion at the instability border will pick up energy while being close to the center of the trap and increase its amplitude. With increased amplitude the secular frequency of the ion is reduced and the ion is pushed back into stable conditions. This delays the ejection of the ion whereas the length of the delay depends on the starting conditions of the ion. This decreases the mass resolution [Franzen, 1993]. By stretching the distance between the end caps or modifying the geometries of the electrodes the pure quadrupolar field is overlayed with weak hexapolar and octapolar (and higher) fields. The sign of the octopole component can be changed by stretching the distance between the end caps (compared to the ideal quadrupole field). A positive octopole component results in an increasing secular frequency with increasing distance from the center and an accelerated ejection of ions from the trap [US5028777A]. Adding higher-order components to the pure quadrupolar field has an additional effect which was patented in 1988 by Franzen et al. [Franzen, 1988]. The motion into the r-direction (i.e., the plane of the ring electrode) and z-direction (i.e., between the end caps) are no longer independent from each other and additional resonance frequencies are introduced into the system. Certain resonance frequencies of this coupled motion have low amplitudes in the r-direction but high amplitudes in the z-direction. If in resonance, the ions pick up energy from the RF field which is transformed into increased amplitudes along the z-direction [Wang, 1993]. This has the important advantage that most ions are focused onto the center of the end caps. A small DC potential can now be used to guide most of the ions to one of the end caps. Thus, a large percentage of ions can actually leave through the holes and reach the detector. For mass selective ejection the main RF is scanned while the auxiliary frequency between the end

caps is kept constant. With increasing main RF amplitude both the amplitude and the secular frequency of the trapped ions increase until the secular frequency of the still-trapped ion with the lowest *m*/*z* value matches the auxiliary frequency. Ions pick up energy from the RF fields which increases mostly the amplitude in the z-direction. The further the ion is away from the center of the trap, the bigger is the impact of the positive octapole component resulting in an even faster energy pick-up. Finally, ions leave through one of the end caps and hit the detector. These scanning schemes are nowadays incorporated in every modern ion trap instrument.

Experiments showed that resolution and sensitivity of this mode of operation increased significantly after increasing the partial pressure of helium in the ion trap. The kinetic energy of the trapped ions is damped by collisions between the ions and the background gas. This reduces the kinetic energy of ions during the trapping which makes them less susceptible to field imperfections close to the surfaces of the electrodes. The kinetic energy is also damped during the RF sweep which reduces the amplitude of the ion motion close to the point of instability. Thus, fewer ions leave the trap close to the boundaries of the stability region [Stafford, 1984].

A further cornerstone of the modern mode of operation for RF ion traps was added in 1987 by the Cooks group [Louris, 1987] The mass-selective instability mode was extended by the possibility of collision-induced dissociation inside the ion trap. Already Paul et al. used resonant excitation of ions for ejection of ions from the confinement field [Paul, 1958b]. Combining resonant excitation with the increased helium background pressure led to extensive fragmentation of the excited precursor ions. During fragmentation the trapping field can be configured to trap a broad mass range, and thus the generated fragments are trapped. Trapped fragment ions can be either detected or used for further fragmentation. This can be further extended by adding isolation steps prior to fragmentation, allowing for an unambiguous assignment of fragment ions. Ions can be isolated and fragmented in numerous cycles prior to detection which allows the exploration of fragmentation pathways over many steps.

The size of the trapping volume of an ion trap limits the maximum number of ions that can be trapped. This limits the signal-to-noise and the dynamic range of a single scan. As it is technically challenging to increase the trapping volume of 3D ion traps, the interest in 2D ion traps grew. In 1988 Dolnikowski et al. modified the collision cell of a triple quadrupole to trap products of ion/molecule reactions [Dolnikowski, 1988]. In this configuration the RF trapping field is still two dimensional and is used for radial confinement. Axial confinement is achieved by static repulsive potentials close to the exits of the multipole electrodes. The repulsive potential at the ends can be created by electrostatic lenses or by different DC offsets of segments of the RF multipole.

All modes of operation originally developed for 3D ion traps can be applied also to linear ion traps. The trapping potential in a linear ion trap has no longer an absolute minimum, but a line of zero potential in its center. Changing the geometry from the hole in the end cap of 3D ion traps into slits in the rods of a linear ion trap enables an efficient ejection of ions using the mass-selective instability mode with or without additional RF fields for ion ejection [Schwartz, 2002].

Yet another variation are two-dimensional ion traps where ions are mass-selectively ejected through slits in the axial direction by resonant excitation [Hager, 2002]. With the combination of all those techniques, modern ion traps can reach resolutions of more than R>30000 FWHM at sufficiently low scan rates [Schwartz, 1991].

The idea of electrodynamic confinement was continued in the 1970s by D. Gerlich who used a variety of configurations for ion beam experiments. Those types of experiments require good control of ion kinetics, which multipole RF fields can provide. Gerlich used the fact that a charged particle in inhomogeneous RF fields is pushed into regions of weaker field. Thus, nearly any number and shape of electrodes can be used for the confinement of charged particles. This was shown by a stacked-ring ion source where ions were guided through a 180° bend [Gerlich, 1971]. Also at this time the first octapole was build. Experiments showed that higher order multipoles are well suited as ion guides. Increasing the number of poles creates multipolar fields with flat potentials in the center. Ions which move close to the center experience a nearly field-free region with limited energy pick-up from the RF field. This makes higher-order multipoles good ion guides and hexa- and octopoles are now widely used [Gerlich, 1992].

One application for electrodynamic trapping is ion spectroscopy. The ability to confine charged atoms and molecules allows sophisticated manipulation such as laser cooling. Laser cooling was proposed by in 1975 by Hänsch and Schawlow for neutrals [Hänsch, 1975] and by Wineland and Dehmelt for ions [Dehmelt 1975; Wineland, 1978]. Sideband cooling with near-resonant laser irradiation was used by Toschek and Dehmelt to confine a small number of ions in a three-dimensional trap [Neuhauser, 1978]. The ions were detected by fluorescence. Further improvements lead to single ion detection in 1980 [Neuhauser, 1980] and the observation of quantum jumps [Nagourney, 1986].

The absorption of photons can also be detected via fragmentation of the investigated ionic species. Nolting et al. used a tunable laser to record UV spectra [Nolting, 2004]. This scheme can be extended by femtosecond laser pulses to probe the excited state lifetime of ions inside an ion trap [Kang, 2004; Nolting, 2007~~)~~]. T. Rizzo combined a 22-pole ion trap built by D. Gerlich with laser spectroscopic methods. The use of a multipole field of that high order made it possible to cool down molecular ions to ~10 K. The vibrational cooling at that temperature results in a dramatic increase of spectrum quality and gives experimental access to rotational and vibrational information of trapped ions [Boyarkin, 2006]. Later, infrared spectra were obtained by IR-UV double-resonance [Nagornova, 2013]. The low temperatures at which ions can be trapped allow for He tagging which is yet another method for obtaining IR spectra. This was realized recently by Roithova et al. [Roithova, 2016]~~ in 2016~~.

Ion traps have become a versatile tool that is nowadays used to investigate a huge range of particles including atomic species, organic molecules, proteins and nanoparticles.

3. Fourier transform ion cyclotron resonance mass spectrometry

3.1. Introductory remarks

Ion cyclotron resonance (FT-ICR) mass spectrometry relies on storage of ions in a high magnetic field combined with a weak electrostatic field. Typically a cylindrical coordinate system is used for reference, and in this system the radial storage is achieved by the magnetic field that is parallel to the axis of rotational symmetry, while the axial storage is achieved by an electrical field, created by the electrodes of the so called ICR "cell", which defines the trapping volume**.** In this cell ions having a velocity component orthogonal to the magnetic field rotate around an axis parallel to the magnetic field lines with a frequency of $\omega = q \cdot B / m$ plus some minor increments due to the electrical field.

While in the beginnings of ICR technology resonant detection or destructive detection where used, current ICR devices use Fourier transform detection. In that case the resonance frequencies of trapped ions are excited by an RF field and afterwards the image current induced by the moving ions on detection electrodes is recorded. The resulting transient signal is digitized, Fourier transformed and converted to masses using a calibration equation, which is in the simplest case just the equation that follows from assuming a homogeneous magnetic field and an ideal quadrupolar electrical field, leading to the second order equation $m = a / \omega + b / \omega^2$, with coefficient a representing mostly the magnetic field contribution and b representing mostly the far lesser contribution of the electrostatic field.. A more detailed introduction to the technology may be found in the "Primer" by A. G. Marshall [Marshall, 1998], or in the 2011 article on FT-MS in general by Scigelova et al. [Scigelova, 2011].

3.2. Early ICR-related research in Germany

Limiting a review of ICR mass spectrometry to research in Germany creates a couple of interesting limitations; not least because German authors did not necessary perform their research here. A notable example with connection to FT-ICR-MS is H. G. Dehmelt, who started research with electrons in Penning traps in 1959 [Dehmelt1976], initiating a long series of measurements of electron spin resonance in Penning traps. That work is definitely a main contribution to the early history of ICR spectroscopy, but has actually been performed in Seattle, Washington, USA.

While Dehmelt and other well-known leaders of early cyclotron resonance mass spectroscopy and Fourier transform mass spectrometry were doing their research in the North America (e.g., [McLafferty, 1971; McIver, 1970; Comisarov, 1974]), the technologies were adopted quickly in Germany. The predecessor of the currently known ion cyclotron resonance devices, the omegatron, employs a measurement principle based on resonant excitation of ions in a magnetic field and detection of the resonant ions impacting on an electrode. It was studied in the 1950's and 1960's (e.g., [Schuchardt, 1960; Reich, 1960]), with a focus on both the methodology and applications like measurement of partial pressures.

Early work on different aspects of ICR was performed by the Hartmann group in Frankfurt am Main. From this group stems also the last review of ICR technology prior to introduction of Fourier transform ICR technology [Hartmann, 1973].

As fitting for a department of physical and theoretical chemistry, the Hartmann group did a lot of theoretical work, e.g., on the relationship between magnetic field homogeneity and mass accuracy [Schuch, 1984]. While this work adopted methods from quantum mechanics, Laukien shortly after this work presented a classical determination of the relationships between magnetic field and mass accuracy [Laukien, 1986].

While first ICR devices relied on electron ionization, the introduction of external ion sources significantly broadened the scope of applications. Research for one of the first external ion sources was done in cooperation with Wanczek from the Frankfurt team and Bruker [Kofel, 1989]. This external ion source was purely electrostatic with gated trapping, i.e., the potential of the ICR cell is temporarily lowered on the side from which the ions are introduced and afterwards raised again. The ion packet or beam is aimed at the cell entrance opening by steering electrodes.

External ion sources brought a breakthrough of FT-ICR for analytical applications. Some of these applications are exemplified in the listing of current FT-ICR groups in Germany below.

Meanwhile, both the Thermo Fisher Scientific as well as the recent Bruker instruments use multipole ion guides for ion injection, rooted in the original work of McIver, Hunter and Bowers 1985. In view of the pulsed nature of the FT-ICR experiment the ions are advantageously stored in an ion trap before they are sent to the ICR cell.

An important use of ICR and FT-ICR instrumentation was study of ion molecule reactions, kinetics and reaction mechanisms. These where dominating the field in the 1970's [Wanczek, 1981] and flourished with the FT-ICR technique.

For the study of reactions, the ions were typically generated by electron ionization. Unwanted ions are then ejected from the ICR cell using resonance excitation of their effective cyclotron frequencies. At the low pressures common for ICR, the ion molecule reactions are of pseudo-first order and progressing slowly. In subsequent experiments the status of the precursor and product ions is observed at various times. For additionally studies reactants can be constantly removed from the ICR cell by resonant excitation during the whole observation period. This method has for example been used for observation of hydrogen exchange reactions between protonated and neutral arenes at a pressure of 10^{-4} Pa [Kuck, 1985] and for the analysis of the reaction mechanisms of radical cations [Nixdorf, 2001].

Similarly, with an external ion source, kinetics may be analyzed at far lower pressures down to the 10^{-8} Pa region. This allows for example the study of the decay of clusters under practically collision-free conditions, showing different thermodynamical stability for different cluster sizes as well as indicating clearly that the fragmentation is driven by the energy input of blackbody radiation from the room temperature environment [Schindler, 1996]. These methods were competing with reaction studies in RF-traps and guided ion beams, both prominently represented in Germany by work of Gerlich et al. [e.g., Gerlich, 1992a; Glosik, 2000], with the RF-traps and guided ion beams frequently being better suited and less costly, especially for studies towards lower energies.

3.3. ICR cells

Besides applications, German scientists drove understanding and technical development of the FT-ICR technology. As an example, the contributions in the field of ICR cell development are summarized below.

The “ideal” design in terms of field geometry is the Penning trap, which has the electrode geometry of a 3D ion trap combined with an additional strong magnetic field parallel to the axis of rotational symmetry of the electrode set. In other words: a homogenous magnetic field, typically of several T, and an ideal quadrupole field. This setup is of continued popularity and relevance in physics, whenever it is important to have a near-ideal relationship between mass and frequency. Gerz et al. discuss the details of such a trap and the influence of various perturbations on the frequencies of ions for a case without image charge detection [Gerz, 1990].

Design of the trapping cells for analytical mass spectrometers is the search for a compromise between the excitation and detection, which in the simplest case call for the field of an infinite plate capacitor, and the perturbation of the cyclotron frequency by the storage field, which calls for an ideal quadrupolar field.

Understanding of the field geometry and properties of the ICR cell is important for practical applications. An example is the calibration of energies for collision-induced fragmentation. In FT-ICR mass spectrometry, collision-induced fragmentation may be effected by excitation of ions with their cyclotron energies. The energy required for fragmentation may be measured by varying the excitation voltage and/or excitation time. For an ICR cell with infinite electrodes or an excitation potential equivalent to that of infinite electrodes the calculation is fairly straightforward and allows a determination of the ion energies as a function of excitation voltage, radiation time, mass and cell diameter. The results have been successfully compared to fragmentation energies from other sources [Sievers, 1996].

The excitation field plays a role for kinetics measurements as well. Driven by the interest in faster removal of intermediate product ions from the ICR cell, miniaturized cells were created allowing for faster elimination from the reaction region [Luebkemann, 2009].

Even quite ideal Penning traps, as used in physics for spectroscopy on stored ions, suffer from nonlinearities. Similar to the mapping of quadrupolar RF ion traps, the nonlinearities of ion confinement in penning traps have been studied in detail [Hübner, 1997]. The main observation is ion loss when the ratio of the axial or cyclotron frequency to the magnetron frequency is an integer number. Under these conditions energy is transferred into the magnetron motion, causing radial loss of ions.

Theoretical investigations by Kretzschmar contribute for example to the understanding of the frequency shifts due to space charge and to a model of signal intensities, including explanation of sidebands in a cylindrical ICR cell [Kretzschmar, 1990; Kretzschmar, 2012].

For high precision physical measurements it may be important to reach a near-ideal Penning (i.e., quadrupolar) potential, despite other limitations on the geometry. For example, a Gabrielse-type [Gabrielse 1989] Penning trap is further optimized for laser beam access and used with FT-ICR detection for fragmentation analysis [Vogel, 2012]. The proposed cell, shown in Figure 1, is conical on the inside, such that a laser beam can be focused onto the center of the cell without touching any electrodes. Owing to a combination of correction electrodes it still has correct-storage field properties.

Figure 1

A bit off-mainstream is the research on simultaneous storage of positive and negative ions. Wang introduced an ICR cell with screens in front of the trapping electrodes of a cylindrical ICR cell, allowing simultaneous storage of positive and negative ions [Wang, 1993]. The need for axially separated trapping regions in such a cell was recognized, and modified designs were suggested in subsequent work [Malek, 1996]. The electrical field and the ion motion in such ICR cells with double-well potentials were studied in detail, including predictions of exact frequencies for ions moving in differing radial and axial regions. Conditions for reactions between positive and negative ions were analyzed [Malek, 1996 and1997]. The observations are compatible with a later work showing that electron capture dissociation works best when the relative energy of electrons is sufficiently low in the reaction zone in an ICR cell with similar field geometry [McFarland, 2005].

More ICR cells are mentioned in the sections below devoted to the two industrial ICR manufacturers in Germany.

3.4. Bruker FT-ICR instruments

The Bruker company was founded in Karlsruhe in1960 by Günther Laukien. While FT-ICR product development was first driven by the Spectrospin AG, which Laukien founded in Switzerland, and later from the Billerica site in the USA, ties to the Karlsruhe and Bremen sites – the latter founded in 1977 by Jochen Franzen as Dr. Franzen Analysentechnik GmbH and acquired in 1980 - were always present.

Collaboration with Prof. Wanczek, first in Frankfurt and later in Bremen included inter alia early work on superconducting FT-ICR [Allemann, 1982] and the development of an external ion source for the Bruker/Spectrospin FT-ICR device [~~(~~Kofel, 1986~~),~~; ~~(~~Kofel, 1989~~)~~].

Many Bruker instruments are equipped with the so called "infinity cell". In the infinity cell the excitation field is extended to the trapping electrodes. In open ICR cells the trapping electrodes are segmented to provide additional excitation electrodes that effectively extend those from the center of the ICR cell. In closed ICR cells the end-plate electrodes are segmented. The curvature of the segment borders follows the desired equipotentials, and the excitation voltages are coupled to these segments. Schematic images can be found in the US patent 5019706 [Allemann, 1991]. The main advantage of the infinity cell is that it corrects the field of the excitation such that the axial component vanishes, reducing coupling of cyclotron motion and axial (trapping) motion during ion excitation. This allows exciting ions to a higher radius with less ion losses.

As an important novel development, the dynamically harmonized Fourier transform ion cyclotron resonance cell is now available from Bruker. Developed by Eugene Nikolaev, this ICR cell is constructed such that – averaged over the rotational motion of the ions - the storage field in the ICR cell is fully quadrupolar. This is achieved by segmenting the excitation and detection electrodes such that lentil- (or leaf-) shaped electrodes (see Figure 2) apply an additional potential that produces the correct field [Kostyukevich, 2012]. Thus, when combined with the infinity cell concept, both storage and excitation potential are close to the theoretical optimum.

The performance is evaluated in a collaborative article between Bruker, the University of Warwick and Nikolaev [Qi, 2012].

Figure 2

The current product Solarix XR uses this ICR cell under the name ParaCell. Various ion sources are available and the system provides a resolving power of 650 000 at *m*/*z* 400 in a one-second scan in absorption mode and resolving power of approximately 520 000 was demonstrated at *m*/*z* 6033 [Li, 2014]. The origin of the instrument is quoted as Bremen, Germany.

From CMS 47 (Beyer, Wanzcek) over Apex (e.g., Apex QE in Kiel and Borstel) to Solarix (e.g., Oldenburg) all instrument generations were recently in use in German FT-ICR laboratories.

The Bremen facility of Bruker Daltonik is quite active in various collaborations showing diverse applications of FT-ICR MS and high resolution and accurate mass spectrometry in general.

Cho et al. [Cho, 2013] of Kyungpook National University (KNU), Korea, working with Korea Basic Science Institute (KBSI), United States Geological Survey, Denver, CO, Climate Change Technology Research Division, Korea Institute of Energy Research (KIER) and Bruker Daltonic Bremen (BDAL-HB) are comparing laser desorption ionization (LDI) and atmospheric pressure photoionization (APPI) for the analysis of shale oils. Inter alia the high resolution is utilized to identify substance classes in van Krevelen plots. LDI is identified to be especially effective in ionizing highly unsaturated compounds.

Further collaborations for example comprise work with Advion and GSK to study ion suppression in imaging [Tomlinson, 2014].

3.5. The Thermo Fisher Scientific LTQ-FT-ICR instrument

Thermo Fisher Scientific (Bremen) GmbH is a site with a long history in mass spectrometry. With origins in 1947 as a part of Atlas-Werke AG the company has a long tradition in magnetic sector mass spectrometry [Brunnee, 1997]. In 1999 the FT-ICR product development responsibility within Thermo Electron Corporation moved from Wisconsin based Extrel FT-MS to the Bremen facility. After evaluation of the existing mature product [Winger et al. 1994] it was decided to start a completely new development with a focus on LC compatibility, with application in proteomics in mind, and ease of use.

These two seemingly straightforward factors provided the critical guidance for the design considerations of the development team.

When it came to ease of use, the ion traps built at that time under the Finnigan brand were the model for the way the users are shielded from the complexity of the instrument. Ideally any scientist should be able to fruitfully run the instrument, not only experts in FT-ICR mass spectrometry.

Compatibility with liquid chromatography was translated to a requirement of being able to acquire at least one mass spectrum per second. Such scan rates would only be possible by making sure that no time is wasted with ion transfer. Thus time-consuming ion capture methods

like collision-assisted trapping were ruled out. The notoriously difficult-to-adjust electrostatic ion-transfer optics were considered incompatible with the goals for ease-of-use of the instrument.

Furthermore, the one-spectrum-per-second acquisition rate means that the ions collected from the ion source within one second have to suffice for a high quality mass spectrum. Thus, in view of the pulsed nature of an FT/MS measurement, a fast ion transfer using a multipole ion guide for ease of adjustment and an ion trapping device that would prepare ions for analysis before transfer were mandatory.

The factory's management team lead by J. Srega, R. Pesch, E. Schröder and S. Horning and the whole R&D team worked closely together with the team in San Jose, CA, which was at the same time developing a new linear-ion-trap mass spectrometer [Schwartz, 2002]. FT-ICR experience in the San Jose team [Senko, 1997] facilitated the joint development process greatly.

The architecture of the instrument with a complete mass spectrometer for ion preparation brought two major features, which were seminal to the success of the technology:

The so-called "automatic gain control" (AGC) was a powerful feature of the instrument. The technology is similar to the AGC in the linear ion trap mass spectrometer. A pre-scan generated with the linear ion trap and integrated over the mass transfer window of the FT-ICR part is used to determine the amount of ions per time unit, and from this the optimal ion filling time is calculated for the analytical scan. The predictability of the amount of ions during the analytical scan of the ICR detector enables mass accuracies in the 1 ppm range [Syka, 2004; Williams, 2007].

Furthermore, the system design allowed ion collection and fragmentation for MS/MS experiments in the linear ion trap while previously collected ions are analyzed in the ICR cell [Malek, 2005a]. This is attractive for proteomics, where the number of hits from a peptide database is advantageously limited when the precursor ion is known with high mass accuracy and the fragments are measured with the far lower resolution but higher sensitivity of the linear ion trap mass spectrometer, giving a "best of both worlds" experience for the combined instrument.

To a large extent even the design of the ICR cell is a consequence of the basic requirement of liquid chromatography enablement. Scan rates of one or more spectra per second, combined with the desire of a wide mass range mean that the ions had to be force-fed into the ICR cell. Even with a high ion-transfer energy there is a significant time-of-flight spread of the ions, meaning that the cell had to be designed such that a long active trapping region with a shallow potential gradient, just high enough to compensate for the energy spread of the ions, is available. Additionally – given that neither time nor gas for collisional cooling were compatible with the design goals – a good field quality over a large region had to be ensured to deliver high quality FT/MS spectra, aiming for quadrupolar field like gradients in the cylinder shell of the ion movement after excitation. This resulted in a five-segment ICR cell with additional end cap electrodes, which combines the excitation and detection homogeneity and the additional degrees of freedom for control of the trapping field of compensated open cell designs [Kuhnen, 1997] with the robustness and field predictability of a closed ICR cell.

Lastly, at the time of the instrument development it was a serious challenge to get the collected mass spectral information out of the instrument at the rate it was generated. For a 7 T magnet, a lower mass-to-charge ratio limit of 50, and 2 bytes per data point, data were generated at a worst

case rate of up to approx. 10 MByte per second. This would have stressed the 100 Mbit Ethernet connections of the time (1 Gbit had just become available but was not widespread) to its limit already for transients. Additionally, it was desired to enable the on-the-spot data-dependent acquisition features of the ion traps for the ICR part as well, which meant that immediate transformation to spectra was on the list of objectives, and shipping spectra instead of - or even on top of - the transient signals would have required an even higher data rate. Slowing down the instrument just for shipping data was not on the agenda. And thus the need for a powerful data handling and compression scheme was born, with all spectral processing performed on the embedded computer of the FT-ICR system. This included the fast Fourier transformation with zero filling and windowing, as well as an analysis of the noise levels, peak picking and determination of mass and intensity. When the processing was done, only mass, intensity, resolution, statistical information about the noise in the spectral region of the peak, and optionally the profile points of identified peaks were shipped to the computer with the user interface and everything else was discarded. Meanwhile, mass and intensity information was made available to the control system of the linear ion trap mass spectrometer for data-dependent decisions. Additionally, the system had the option to start processing early with only a first fraction of the FT-signal and deliver lower resolution mass and intensity information for data dependent decisions while waiting for the remainder of the transient to arrive and commencing the main processing [Malek, 2005].

In 2003 the product shown in Figure 3 was introduced [Horning, 2003], featuring a resolution of 100 000 at m/z 400 with one scan per second and up to 5 Hz at lower resolution, driven by the innovations in ion injection [Malek, 2004] and data compression.

Figure 3

Options that were introduced later include infrared multi-photon dissociation (IRMPD) and electron capture dissociation (ECD).

As a further improvement the LTQ-FT Ultra featured an additional grid electrode, shown in Figure 4, for ion excitation, giving improved excitation field properties, which in turn allows for a rapid ion excitation to a higher cyclotron radius for maximum sensitivity. Some of the "Ultra" instruments were equipped with high-field magnets up to 12 T.

The LTQ-FT instrument was a huge commercial success, but with the Orbitrap mass spectrometers developed in the same facility it became clear that – especially when coupled with liquid chromatography – the Orbitrap analyzers were going to be able to deliver the same or better resolution per unit time as compared to an FT-ICR instrument, especially at higher m/z values, and could in the long run become a serious contender for routine highest resolutions as well. Moreover, further mass range limitations caused by the injection of ions into the magnetic center of a superconducting magnet are not an issue for Orbitrap mass spectrometers.

Current Orbitrap mass spectrometers have shown the same one-million mass resolution as the LTQ-FT Ultra instrument was specified to deliver. Additionally, without the size and expense of the magnet and especially the cost for coolants or cooling, an Orbitrap instrument delivers performance at a significantly lower total cost of ownership. Therefore, the ICR product line was discontinued a few years ago in favor of the Orbitrap technology.

Figure 4

3.6. Selected examples of FT-ICR applications

This section gives a short overview of applications recently pursued by groups in Germany or with German participation, using FT-ICR mass spectrometers. A detailed review of activities would exceed the scope of this review by far, so the following is more a pointer for those interested and an opportunity for networking. Focus is on fields where the instrumentation provides specific advantages due to the storage method or ultra-high resolution.

Gas-phase ion chemistry has been one of the oldest fields covered by FT-ICR mass spectrometry. Typical applications are determination of rate constants of unimolecular reactions and ion-molecule reactions. The variety of fields covered illustrates the versatility of the technique, going from (inter alia) unimolecular decay of metastable ions [Wittneben, 1990] over extensive studies of water clusters [Niedner-Schatteburg, 2000] to acid-base reactions in the gas phase [Mormann, 2006].

The FT-ICR technology may be used to study the structure of molecules by various fragmentation methods [Hahn, 2013; van der Linde, 2013; Hovorka, 2013]. Another major direction is the study of reactions and the determination of energies by kinetic studies, e.g., by Bhunia et al. [Bhunia, 2012; Karpushkin, 2013] and Fraschetti et al. [Fraschetti, 2012; Siehl, 2013]. Such studies make use of the unique trapping and ion manipulation techniques available in FT-ICR MS and are a domain which cannot be easily transferred to Orbitrap technology. The techniques mentioned at the end of section 3.2 are important alternatives, though.

Life Sciences, including proteomics and related applications, are one of the main application fields using FT/MS instrumentation. A substantial fraction of the FT-ICR related publications is in this field. The high resolution and mass accuracy is a valuable tool for reliable substance identification and helps getting meaningful hits in database search. The early adopters and, of course, many current users of the Thermo Scientific LTQ-FT mass spectrometer belong to this field and also all FT-ICR product lines of Bruker Daltonics were and are used in this field. Not least due to the progress in the ease-of-use of these instruments, proteomics users tend to use the instrumentation just as a tool. The focus is on the underlying life science problem, and the mass spectrometer is just a very high end laboratory appliance that is able to generate the information desired by the scientists. Indirectly this also means that many publications using FT-ICR mass spectrometers may be missing here, when the use of the technology is not apparent, for example when it is not mentioned in the abstract or keywords. In many, but not all of these applications FT-ICR instrumentation can be replaced with Orbitrap mass spectrometers.

Major directions are bottom-up proteomics studies, where the analytes are digested proteins, as demonstrated by Heuveling et al. [Heuveling, 2014].

Quantitative proteomics is a developing field, including first attempts within other studies [Hessling, 2013], metal labelling of proteins [e.g., El-Khatib, 2014] and a study by Stavenhagen et al. [Stavenhagen, 2013] that systematically determines the mass spectrometric response to peptides and glycopeptides. Besides the protein/peptide targets, other compounds in various organisms are studied, from microbial pathogens [Gisch, 2013] or cell constituents [Carillo, 2013; Zehethofer, 2010], over compounds in barley seeds [Gorzolka, 2014], metabolic

fingerprints of funghi with direct-infusion ESI-FT-ICR mass spectrometry and PCA [Heinke, 2014].

Another life science field recently addressed with FT-ICR is sports doping analysis [Thevis, 2012; Kiss, 2013], targeting metabolites of various dopants.

While, strictly speaking, a subset of the life sciences, the interest in organic content in water bodies, including pollutants, is sufficiently widespread to consider it a separate community. It is also another domain where Orbitrap instruments are slowly replacing FT-ICR instruments due to the high resolution used. Examples for applications are the analysis of proteins in wastewater [Amado, 2014] and a study of chlorination of organic matter in connection with disinfection [Lavonen, 2013].

The high number of compounds found during study of marine-dissolved organic matter [Flerus, 2012; Lechtenfeld, 2013] pushes FT-ICR data evaluation to its limits, such that scientists write their own specialized data evaluation software and/or use methods from fossil-fuel analysis. Van Krevelen plots, exemplified in Figure 5, are used to visualize the various substance classes by utilizing the high mass accuracy of the instruments for the determination of reliable elemental compositions.

Figure 5

Petroleomics were made popular by the Marshall group at NHMFL in Florida [Marshall, 2008], representing an area of analysis where the ultra-high resolution capabilities of FT-ICR mass spectrometry are of utmost importance.

Despite advanced separation techniques (see, e.g., [Gaspar, 2012]), the peak density is immense. Ultra-high resolution helps to keep peaks apart and, thanks to the high mass accuracy, mass-defect systematization and elemental composition assignments are excellent. A popular tool in petroleomics is the Kendrick mass plot based on [Kendrick, 1963], which normalizes the mass scale to the mass of the CH_2 unit and then plots the decimal part of the result over the integer mass. The article published by Hughey et al. is a typical example [Hughey, 2001]. Compositions with the same modification appear as horizontal rows in a Kendrick plot. Based on elemental composition calculations, the populations of different compound classes may be characterized and, for example, the double bond equivalents (i.e., a measure of unsaturation of the hydrocarbons) may be determined. Besides the intuitive visualization, another advantage of the method is that the horizontal grouping created by the arrangement helps to remove ambiguities in elemental composition.

Analytical targets besides crude oil components like asphaltenes [Jarrell, 2014] are coal [Kroll, 2012] and even scrap tires [Rathsack, 2014a].

4. Orbitrap Mass Spectrometry

4.1. First steps toward Orbitrap mass spectrometry

The history of Orbitrap development is a positive example of scientific globalization that started to gain pace in the last decades of 20th century and even accelerated in the new millennium in spite of political disruptions and crises of the last decade. Originally started by Russian, British and Australian scientists in the UK, the initial Orbitrap research allowed in a short time to get a glimpse of future performance of the electrostatic trap technology [Makarov, 2000; Hardman, Makarov, 2003; Makarov, 2013] and even to bring it into capable hands of Prof. R. G. Cooks' team in Purdue University, thus facilitating promising additional directions of research [Hu, 2005; Perry, 2008].

Corporate re-structuring resulted in transplanting this research together with the core team to the Bremen factory of Thermo Fisher Scientific (then ThermoFinnigan MAT) in Northern Germany. Being spread over years and starting in 2002, this transfer succeeded due to wholehearted support of the factory's management team lead by J. Srega, R. Pesch, E. Schröder and S. Horning. It also greatly benefited from another international project that was just about to come to fruition: integrating a linear trap developed in San Jose, CA [Schwartz, 2002] and an FT-ICR analyzer [Syka, 2004] from Madison, WI. This integration process required complete redevelopment of FT-ICR technology, as described in the previous chapter of this review, by a newly assembled project team in the Bremen factory. The subsequently established Orbitrap project team included many participants of the LTQ-FT-ICR effort and became even more international. Combination of innovative technology with decades of instrument development experience, processes and know-how allowed this team to launch a commercial LTQ Orbitrap instrument already in 2005.

This instrument laid the foundation for all subsequent serial instruments and implemented the following basic principles of Orbitrap technology [Makarov, 2010]:

1. The Orbitrap analyzer is implemented as a three-electrode construction (Figure 6) with just two functions: capture/excitation of ions and detection. The former function is performed by a voltage ramp on the central electrode while the latter is achieved by split outer electrodes. Such "separation of powers" allows to keep electronics and mechanics as simple as possible, resulting in better manufacturability. It also means that the trap is used just as an accurate mass detector and not as a self-contained MS^n device like a classic Paul trap or FT-ICR instruments. On the other hand, the electrostatic nature of the field eliminates the need for strong RF and magnetic fields [Makarov, 2000].
2. Ions are injected into the Orbitrap analyzer from an external accumulation device, typically implemented as a bent RF-only multipole filled with a bath gas for collisional cooling of the ions (C-trap). Fast ramping down of RF-voltage and pulsed electrical acceleration are employed to form pulsed ion packets focused onto the entrance to the analyzer.
3. Ion packets are captured using the principle of "electrodynamic squeezing", wherein ions experience a steady increase in electric field strength as they enter the trapping field. Once inside the field, the ions cannot return back to the point of entry because by the time of return a noticeable potential barrier between them and the entrance point gets formed. The rate of field ramp is matched to the mass range of the ions stored in the C-trap which in turn is regulated by the amplitude of trapping RF voltage.

4. Ion packets are introduced into the trap not along its center ("equator") but at some distance from it, so that they experience a considerable axial electric field as they enter the trap. Orbital angular momentum on injection is selected to match the radial field so that the trajectory inside the trap follows an approximately circular spiral. This initiates "excitation by injection" without the need for any additional excitation and also enables good phase coherence. The initial point and moment of entry defines the final axial amplitude of the ion trajectories.
5. Measurement of the ions' *m*/*z* values is done based on the frequency of axial oscillations of the ion packets in the form of rings. They are detected via the image current induced on the split outer electrodes.
6. Four-stage differential pumping enables seven orders of magnitude pressure drop over as many centimeters of distance, thus keeping the C-trap/Orbitrap design compact and drastically reducing *m*/*z*-dependent transmission effects. Because of the linear geometry of ion beam on the exit from the C-trap, slit apertures of diminishing widths are used (from 1 to 10 mm), which requires pumping speeds in the range of 20-100 L/s in each pumping port.
7. The number of ions in the trap needs to be tightly controlled in order to minimize space-charge effects. Such control is performed by external "complementary" devices such as a preceding mass analyzers, charge detectors, and ion gates in a way that had been first established in LTQ-FT instruments.

Figure 6

4.2. First commercial instrumentation

In the very first commercial instrument, the linear trap LTQ unit performed the function of such self-contained "complementary" device due to its very high sensitivity, refined control of the number ion ions, short cycle time, and MS^n capability. Depending on the requirements for the analysis, the two analyzers in LTQ Orbitrap instrument can be used independently or in concert [Makarov, Denisov, Kholomeev, 2006]. Typically, this instrument utilized the Orbitrap analyzer for wide mass range, high resolution/accurate mass (HR/AM) spectrometry and identification of precursor *m*/*z* values for subsequent fragmentation, while the linear ion trap was used for acquiring MS/MS scans of precursor ions selected in the so-called data-dependent mode on the basis of the previous Orbitrap spectrum or of the initial part of the running transient. This reflected the relatively low sensitivity and speed of Orbitrap analyzers at the time. Nevertheless, the newly introduced ability to get low-ppm mass accuracy starting practically from the limit of detection [Makarov, Denisov, Lange, 2006] became a game-changer for proteomic, metabolomic and forensic analysis.

Further technology development concentrated mainly in the Bremen factory of Thermo Fisher Scientific, while development of its applications proceeded worldwide at a rapid pace.

It is worth noting that some of the very first and at the same time most important applications of the new technology were demonstrated by closely-located collaborators within Germany. The group of Prof. M. Mann in Martinsried (near Munich) applied it to the SILAC proteomic workflow, previously run on an LTQ-FT instrument [Olsen, 2005], and later to whole-proteome

sequencing [de Godoy, 2008], while the group of Prof. W. Schänzer and Prof. M. Thevis in Cologne started using it for studying the metabolism of small-molecule drugs [Thevis, 2005] and later of anti-doping analysis [Thevis, 2011]. With the current list of papers using Orbitrap technology counting in many thousands, this review focuses mainly on the development of the technology. For analytical applications the reader is referred to other overviews [Scigelova, 2009; Scigelova, 2011; Scigelova, 2013; Eliuk, 2015].

Since then the analytical capabilities of the LTQ Orbitrap instrument were expanded in several distinct ways.

The use of the C-trap for delivering the ions into the Orbitrap analyzer was complemented by several novel modes of operation. For example, the C-trap became increasingly used to accept multiple fills, wherein an injection of a fixed number of ions of a known compound can be followed by injection of one or more pulses of analyte ions. The combined ion population is then injected simultaneously into the Orbitrap analyzer. This approach was initially introduced for a robust internal calibration of each spectrum, with r.m.s. errors below 1 ppm [Olsen, 2005]. For proteomic samples, coelution of hundreds and even thousands of peptides in the same spectrum, with multiple charge states of the same peptide present simultaneously, was found to be useful for improving the mass precision down to few hundreds of part-per-billion [Cox, 2009].

Another intriguing capability of the C-trap arises from the ability to store together multiple injections of ions fragmented or selected at different conditions, so that all this potpourri-like ion population can be then measured in a single Orbitrap spectrum to provide better sequence coverage or parallelize different measurements.

The C-trap can be also considered as a useful T-piece that allows interfacing to additional devices. This versatility provided by the C-trap has been extensively utilized for later extensions of the LTQ Orbitrap instrument.

Insertion of a collision cell following the C-trap in the LTQ Orbitrap XL instrument has opened a route to higher-energy collisions (with energies higher than those achievable in the linear ion trap), hence the term higher collision energy dissociation (HCD) [Olsen, 2007]. Ions are allowed to pass through the C-trap, enter an acceleration gap and then fragment in an RF-only quadrupole collision cell in a way similar to the fragmentation in triple quadrupole or quadrupole time-of-flight instruments. Fragment ions are trapped and cooled inside the cell, and then sent on a return path to the C-trap from which they are injected into the Orbitrap analyzer for detection in a usual manner. This allows the collection of all fragments without any low-mass cut-off. Analysis of immonium ions, quantitation with iTRAQ™ or TMT™ labels, de-novo sequencing of peptides, and building highly informative fragmentation spectra libraries are just a few application areas that benefit from such an HCD collision cell.

A further important development was the addition of electron transfer dissociation capabilities [McAlister, 2008] where the C-trap was used even more adventurously for ion transit. For ETD application, reagent anions (such as fluoranthene) are produced by a chemical ionization source located behind the HCD collision cell. They pass through the HCD cell and the C-trap into the linear trap where ion-ion reactions with peptide cations take place. The resulting peptide fragment ions can be analyzed by the linear ion trap or transferred to the C-trap and then to the Orbitrap analyzer, thus offering a choice between high sensitivity and high mass accuracy and resolution. The ETD technique allows for the analysis of a much greater variety of post-translational modifications than collisional-induced dissociation (CID) or HCD do, providing in

many cases an unambiguous identification and localization of phosphorylations, methylations, acetylations, glycosylations, and other generally fragile modifications within the peptide sequence. Owing to the high resolving power and mass accuracy of the Orbitrap analyzer, the ETD approach can be successfully applied not only to peptides, but also to small- and medium-sized proteins. The resulting instrument configuration driven by a powerful data-dependent 'decision tree' software allows the combination of CID, HCD and ETD fragmentation techniques within one single system [Swaney, 2008].

Addition of a MALDI source operating at reduced pressure proved to be another important extension of the LTQ Orbitrap capabilities. Trapping in gas minimizes issues related to unimolecular dissociation due to the high laser power used for desorption. As a consequence, a smaller number of shots could be employed to produce greater ion populations [Strupat, 2009]. This allows for a dynamic range of many thousands just in a single Orbitrap scan. At the same time, high transmission to the Orbitrap allows for excellent sensitivity. Important applications include peptide mass fingerprinting, tissue imaging, and LC-MALDI.

A number of atmospheric-pressure ion sources (API) has been interfaced to this and later Orbitrap instruments, such as an atmospheric-pressure MALDI, laser diode thermal desorption (LDTD), desorption electrospray ionization (DESI), inductively coupled plasma (ICP), Direct Analysis in Real Time (DART), and others. Filtering devices were also successfully used, for example High-Field Asymmetric waveform Ion Mobility Spectrometry (FAIMS). These extensions enhanced and extended the utility of the instrument.

The next generation change took place with the introduction of the LTQ Orbitrap Velos in 2009, where a number of innovations were introduced to increase sensitivity and scan speed [Olsen, 2009]: a stacked ring RF ion guide (so called S-lens) and a dual pressure ion trap configuration with accelerated scanning and reduced overhead times between scans. Ion injection times for MS/MS were predicted from preceding full scans (predictive AGC) instead of performing automatic gain control scans prior to each MS/MS spectrum. Altogether, these improvements routinely enabled acquisition of up to ten ion trap MS/MS spectra per second. This instrument also featured an improved HCD cell with reduced ion losses and higher-temperature bakeout of the Orbitrap analyzer for improved top-down analysis.

The last and the top-performing member of LTQ Orbitrap instrument family became the Orbitrap Elite™ mass spectrometer [Michalski, Damoc, Lange, 2011], where a new generation of Orbitrap analyzers was used for the first time. By employing a compact, high-field Orbitrap analyzer, the observed frequencies practically double. The new design of the analyzer was developed on the basis of earlier research [Makarov, 2009] and had outer electrodes scaled down by factor of 1.5 and the central electrode by factor 1.2 with respect to the previous trap (Figure 7). The smaller size combined with new lower-capacitance transistors of image current preamplifier enabled a by 40% higher sensitivity of detection.

Figure 7

In addition, an enhanced Fourier transform (eFT™) algorithm [Lange, 2014] further doubled the resolving power to 240,000 at m/z 400 for a 768 ms transient. Thus, overall 4-fold improvement relatively to the original trap was demonstrated. This algorithm incorporates information about

phases of ion oscillations which are precisely defined due to the built-in "excitation-by-injection" mechanism. Both of these innovations required rigorous improvements in adjacent ion optics, preamplifier, and machining accuracy of the Orbitrap electrodes. In parallel, robustness of the ion transfer optics and the MS/MS acquisition speed of the dual linear ion trap were improved in this instrument.

This instrument was used then for pushing frontiers of Orbitrap mass spectrometry even further. For example, using a carefully selected and manually tuned analyzer it became possible to obtain high-quality spectra with good isotopic accuracy at resolving powers in excess of one million [Denisov, 2012], which was possible before only in the FT-ICR world. This progress also was used to achieve isotopic resolution of intact antibodies at 150,000 Da mass [Shaw, 2013] and in a separate study, for top-down analysis of these important biomolecules [Fornelli, 2012].

4.3. Recent developments

Appearing originally a bit in the shadow of the LTQ Orbitrap family, a non-hybrid Orbitrap mass spectrometer, the Exactive instrument, made its debut in 2008-2009. This bench-top machine featured a stand-alone Orbitrap mass analyzer with an atmospheric-pressure ionization source and, having no mass selection capabilities, was intended for high-resolution screening applications [Bateman, 2009; Geiger, 2010; Thomas, 2012]. The ion source interface was followed by a bent 90-degree RF-only flatapole that separated the ions from the gas jet and rendered the instrument less deep. For the first time, a multi-stage ultra-high vacuum (UHV) turbomolecular pump was used to evacuate the aluminum Orbitrap chamber down to pressures in the 10^{-10}-10^{-11} mbar range. Other than that, the layout of the C-trap/HCD cell/Orbitrap combination remained unchanged as compared to the LTQ Orbitrap Velos instrument. The simplicity of the layout was reflected in the simplicity of acquisition methods available: just a wide mass range mode or all-ion fragmentation mode when all ions of wide mass range are subjected to HCD in a collision cell. Eventually, this mass spectrometer got an S-lens and bent flatapole replacing the tube-lens interface (like in earlier LTQ Orbitrap instruments), ~~,~~ and appeared in 2012 under the name Exactive Plus. The instrument became the foundation for the development of the Q Exactive mass spectrometer that turned out to become the most successful and numerous high-resolution instrument so far.

The Q Exactive instrument was unveiled in June 2011 and differed from Exactive just by addition of a quadrupole mass filter in order to add selectivity. Other important modifications included S-lens, eFT signal processing, a less contamination-prone bent flatapole and, being crucial for the ion population control, a charge detector used to correct for part of ion current left undetected within short Orbitrap pre-scans [Michalski, Damoc, Hauschild, 2011]. Another important innovation was decoupling of the C-trap filling from the Orbitrap acquisition: these two processes could now run in parallel, thus significantly increasing the duty cycle of the analysis, frequently to levels well above 90%.

This instrument rapidly became the workhorse of not only -omics sciences but also of HR/AM analysis in forensic, toxicology, environmental laboratories. This was accompanied by expansion of the available models. First, the Q Exactive Plus received a hyperbolic-rod quadrupole filter with pre- and post-filters as well as pre-filtering of precursor ions in the source optics for higher robustness. It was followed by the new flagship, Q Exactive HF, featuring high-field Orbitrap analyzer and spectrum acquisition rates up to 20-25 per second [Scheltema, 2014]. Also, a

feature-reduced but ruggedized variant of the Q Exactive instrument, Q Exactive Focus, was released for routine analysis [Grund, 2016].

One of the most interesting examples of interplay between capabilities of instrumentation and new applications became the field of native mass spectrometry. Until recently, it was dominated by the Q-TOF technology that looked naturally suited for the analysis of high-*m*/*z* ions of protein complexes. However, improvements of the vacuum, ion trapping and processing gradually made it possible for Orbitrap mass spectrometry to enter this field. As the result of the collaboration between the Bremen factory and the group of Prof. A. Heck at Utrecht University, the Exactive Plus EMR mass spectrometer became the test-bed for extension of Orbitrap mass spectrometry towards higher and higher mass-to-charge ratios, making it possible to analyze protein complexes under native conditions [Rose, 2012; Rosati, 2012]. In these papers, it was established that the increase of the *m*/*z* values had the unexpected consequence of reducing the center-of-mass collision energy of the ions in the trap and therefore decelerating the loss of signal by collisions. This in turn increased the resolution of the analysis and allowed for the detection of individual ions of protein complexes. Owing to the trapping in the HCD cell and in the C-trap, more effective desolvation could be achieved. Later, the selection by modified quadrupole mass filter was added [Dyachenko, 2015] to enable MS/MS capabilities and, even later, pseudo-MS^3 experiments that allowed the operator to break complexes down to subunits and then perform top-down analysis of these subunits for their identification [Belov, 2013; Skinner, 2016]. In all these experiments, the initial desolvation was carried out by applying electrical acceleration in the fly-through mode following expansion from the atmosphere into the vacuum [Gault, 2016]. However, the real advance of desolvation that enabled squeezing the mass distribution unprecedentedly close to isotopic distribution became the so-called in-source trapping [Belov, 2015]. In this approach, ions are intermittently trapped immediately after expansion into the vacuum, and the entrance energy into the trap is selected high enough to enable complete desolvation. If desired, this allows even for the removal of outer non-covalently bound layers such as lipid rafts or micelles. After trapping, the ions are released into downstream ion optics and the process is repeated at the rate of several hundred cycles per second, such that the C-trap keeps receiving a quasi-continuous ion beam that could be regulated in the normal manner.

Coming back to the theme of instrumentation development, it should be noted that Q Exactive mass spectrometers became used essentially as building blocks in other mass spectrometers of Thermo Fisher Scientific that were developed in the San Jose and Austin factories. Orbitrap Fusion [Senko 2013] and Fusion Lumos [Martins, 2016] became the first tribrid instruments in history of mass spectrometry, enabling parallel operation of three different mass analyzers in one integrated device. The variety of experiments possible on these machines expanded greatly as compared to the previous top-tier Orbitrap Elite and include for example highly-multiplexed isobaric tagging (e.g., with TMT labels) with synchronous parallel selection [McAlister, 2014], protein cross-linking using MS-cleavable cross-linkers [Yu, 2016], EThcD [Brunner, 2015] and other approaches.

The Q Exactive GC [Mol, 2016] and Exactive GC instruments opened a new chapter in the long history of marriage between gas chromatography and mass spectrometry. These systems combined HR/AM with sensitivity and linearity that even in the full mass range mode was at par with triple quadrupoles operated in SIM mode. This combination allowed new capabilities in both targeted and untargeted GC-MS analysis in a diverse range of applications, such as

pesticide residue analysis; persistent organic pollutants screening, impurity profiling of pharmaceutical intermediate compounds, etc.

Breakthroughs in increasing transmission of atmosphere-pressure interface (API) over the last 10 years enabled a revolution in ion sources operating at ambient conditions [Smoluch, 2016; Ferreira, 2016]. Special mentioning in this regard deserves atmospheric pressure matrix-assisted laser desorption/ionization (AP-MALDI) source developed by Prof. B. Spengler's group in Giessen University [Römpp, 2013]. This source allowed them to analyze tissues at atmospheric pressures with spatial resolution down to only few micrometers. When combined with HR/AM analysis on the Q Exactive instrument, metabolite profiling became possible with unprecedented detail.

Another example of atmospheric pressure sources became the interface between GC and Q Exactive instrumentation as developed by Prof. T. Benter's group at Wuppertal University [Kersten, 2016]. This interface utilized atmospheric pressure photoionization (APPI) for ionization of volatile compounds in GC peaks and demonstrated sensitivities down to femtogram-on-column levels.

Significant collaborative research was also directed towards understanding fundamentals of ion motion inside the analyzer itself [Grinfeld, 2015], demonstrating the need for careful balancing of electrode tolerances.

Wide acceptance of the Orbitrap analyzer by the scientific community in life sciences and analytical chemistry did not go unnoticed by other fields of research. One of the most long-term and promising applications of the technology promises to become space exploration where small size and electrical simplicity of the analyzer and data acquisition hold promise of revolutionizing the quality of in-flight mass analysis [Cottin, 2010; Briois, 2016].

Also, the technology could be used in combination with light spectroscopy of cold ions for the analysis of molecular structures [Kopysov, 2015], allowing for example separation and quantitation of isomers [Kopysov, 2016]. These experiments make a significant step in fidelity of structure determination comparing, for example, even to such promising fragmentation methods as ultraviolet photodissociation [Madsen, 2010] already combined with Orbitrap mass spectrometry [Fort, 2016; Tamara, 2016]. It should be noted that in such combinations the Orbitrap analyzer remains just a detector while manipulations with ions are performed in external linear radiofrequency traps as described in Section 2. With Orbitrap detection, these traps do not need to be capable of mass analysis and this opens a lot of possibilities with ion processing and storage using not just single RF traps but even arrays of them.

Further progress of Orbitrap technology is inextricably linked with continuing improvements in all its aspects, from analyzer design to methods of ion manipulation and signal processing, and its combination with new ion sources and separation techniques. While the former activity continues to reside with the core scientific and engineering group in Bremen, the latter increasingly ensues in collaborations with universities and small companies both in Germany and around the world.

4.4. Other types of electrostatic traps

As was shown previously [Makarov, 2010], the Orbitrap analyzer is just one representative of a broader class of electrostatic traps, with the total variety of trap variants reaching double-digit numbers.

The harmonic nature of the axial oscillations enables the Orbitrap mass analyzer to provide, for a given size, the highest frequency and the highest quality of ion focusing within this variety, making it most suitable for image current detection. However, more complicated and elaborate designs such as the Cassini trap [Köster, 2009; Köster, 2014] were also proposed for mass analysis with image current detection. This trap features at least two central electrodes and, similarly to the Orbitrap field, sustains harmonic axial oscillations. While offering some advantages for injection, for a similar analytical performance such a trap would require complicated 3-dimensional machining at the same tolerances as achieved in the 2-dimensional Orbitrap machining.

Acceptable analytical performance could be also achieved at the lower quality of focusing than ideal harmonic oscillations, for example in electric fields providing first- or second-order independence of period of oscillations on initial ion parameters like ion energy, initial position, etc. This also means that every multi-reflection or multi-deflection TOF analyzer could also be used with resonant excitation as initially shown in an early US patent [Melzner, 1965], or with image current detection as shown later [May, 1992]. While such analyzers with secondary electron or ion emission detection belong to TOF-MS and therefore lie outside of the scope of this review, their incarnations with image current detection are worth mentioning as they steadily appear in research literature in experiments in physics (see, e.g., a review by [Andersen, 2004]) or high-mass ions [Benner, 1997]. One of major limitations of such traps appears to be non-linear interaction of field non-linearity with the space charge of ions ("self-bunching" effect [Strasser, 2003]), resulting in severe distortions of isotopic ratios [Zajfman, 2003]. While acceptable in most of physical experiments, this problem generally affects the applicability of such non-harmonic mirrors to analytical applications.

5. Conclusion

Modern trapping mass spectrometry goes far beyond the original separation between "tandem in space" and "tandem in time" mass spectrometers [Johnson, 1990] and also beyond the scope of this fairly focused review.

It rather starts to bear similarity to modern computers where ion traps perform the role of memory cells. These cells then ensure lossless operation of processors, in this analogy represented by beam analyzers. This evolution ensures continuing progress of trapping MS in incarnations that go beyond the three distinct classes of ion traps described above and gives us a hope that new classes of electrostatic and radiofrequency traps will emerge in the coming years. They might not necessarily come in the form of high-resolution analyzers but rather as trapping arrays and distributed networks tightly integrated with other types of mass analyzers and in-vacuum separation techniques.

This promises to open new horizons in sensitivity, speed and depth of analysis, thus ensuring continuous progress of mass spectrometry for the benefit of our entire humanity.

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Figures

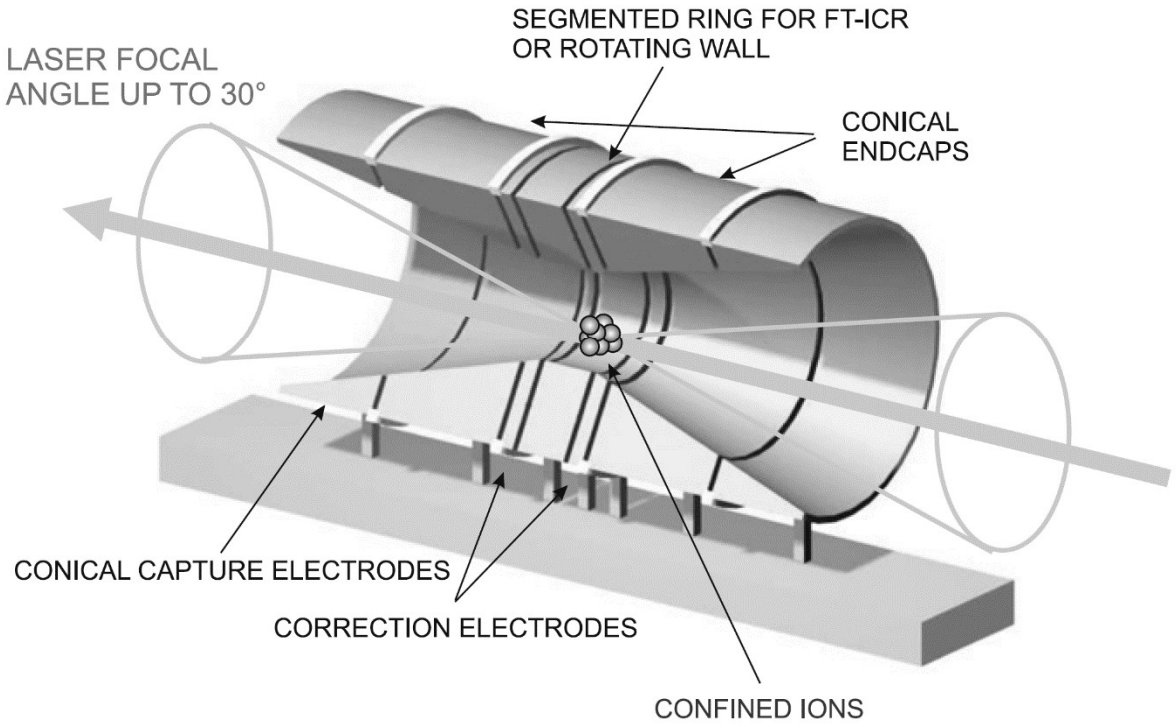

Figure 1. An ICR cell [Vogel, 2012], with conical endcaps, for accommodating a laser beam, allowing spectroscopy on stored ions. The grey arrow symbolizes the laser beam, which is parallel to the magnetic field. Segmentation of the central ring into excitation and detection electrodes is not visible in the image. The axial segmentation of the cell into various rings with different voltages helps creating the desired storage field.

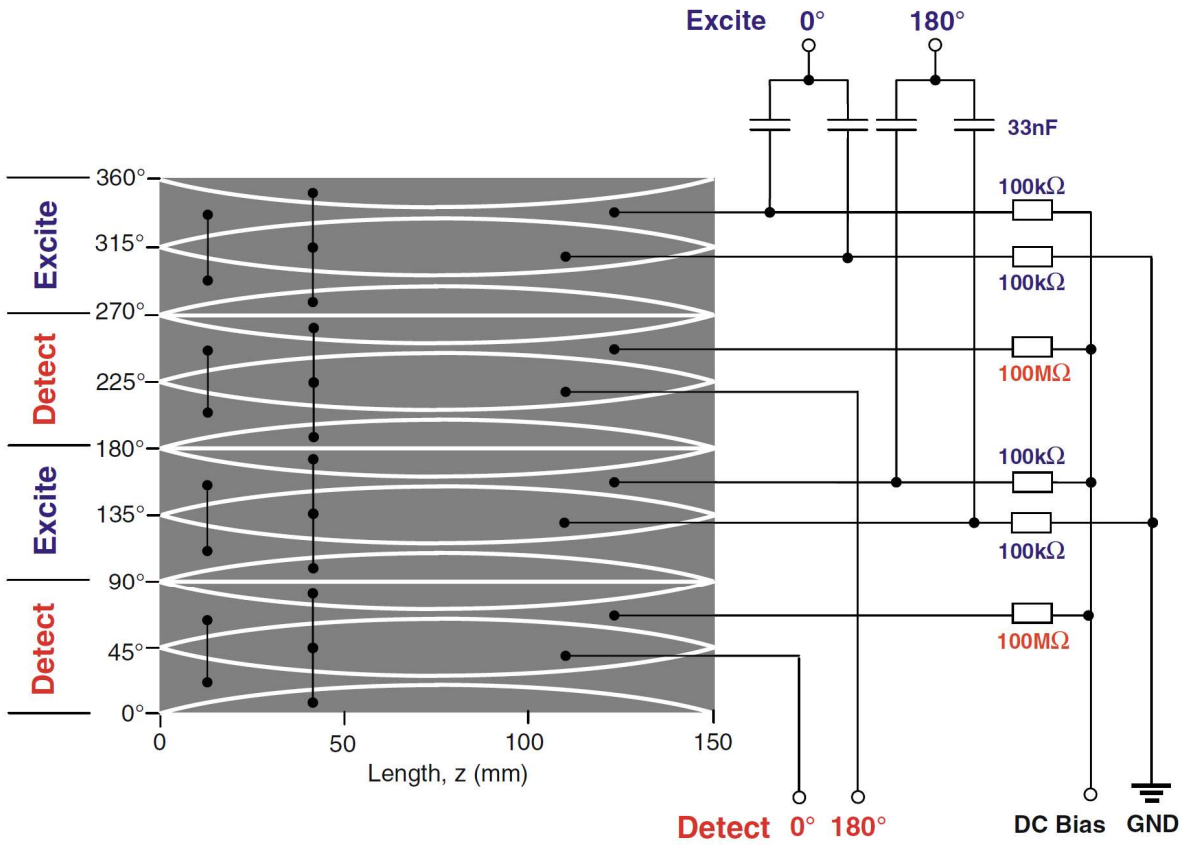

Figure 2. Wiring diagram of the dynamically harmonized cell. The electrodes on the outer cylindrical border are shown "unrolled" (image from [Nikolaev, 2011]). The creation of the electrostatic trapping field is easiest imagined by assuming the 'leaves' being at DC ground and the 'surrounding' electrodes and the end plates (not shown) at a common DC trapping voltage. The resulting warped electrostatic potential distribution averages out to a nearly ideal quadrupole field for ions moving on a cylindrical orbit concentric with the cell's axis of symmetry. The shape of the "leaves" defines the exact average potential distribution.

Figure 3. The LTQ FT mass spectrometer (reprinted with permission of Thermo Fisher Scientific). The devices on the dark 'tray' are a liquid chromatography system (left) and an LTQ linear ion trap mass spectrometer (right). The large housing behind the LTQ contains the superconducting magnet. All ancillary aggregates, such as the vacuum system, pumps, electronics are within the covers. The user interaction with the hardware is focused on sample introduction and few essential status displays. The control is implemented via a separate computer (not shown).

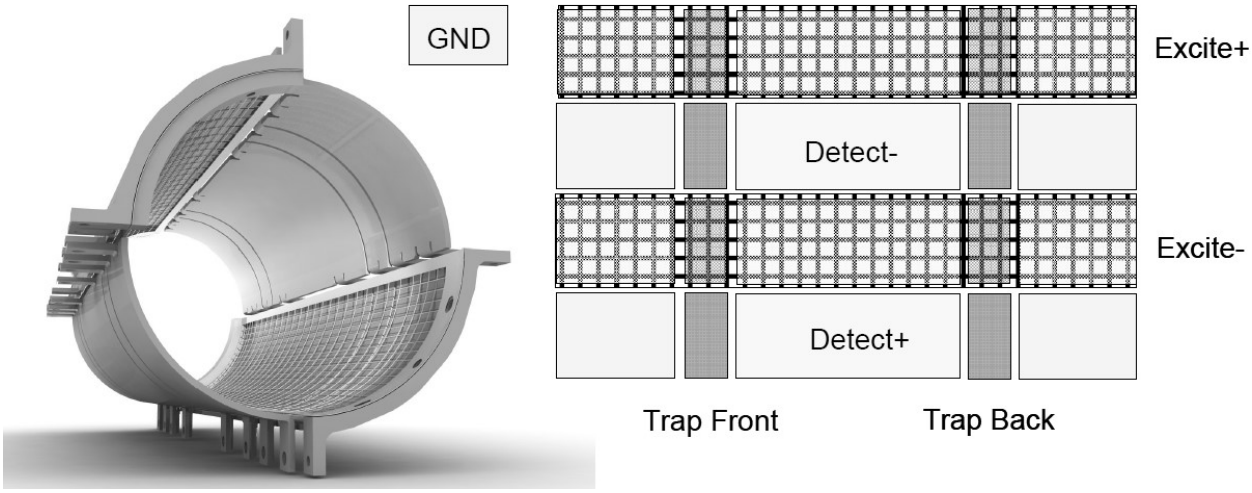

Figure 4. The trapping cell of the LTQ-FT Ultra creates an optimized excitation field by use of grids that span the whole length of the ICR cell (reprinted with permission of Thermo Fisher Scientific). The left image shows a 3D view of the grids and the right image is an „unrolled“ schematic representation of the electrode configuration.

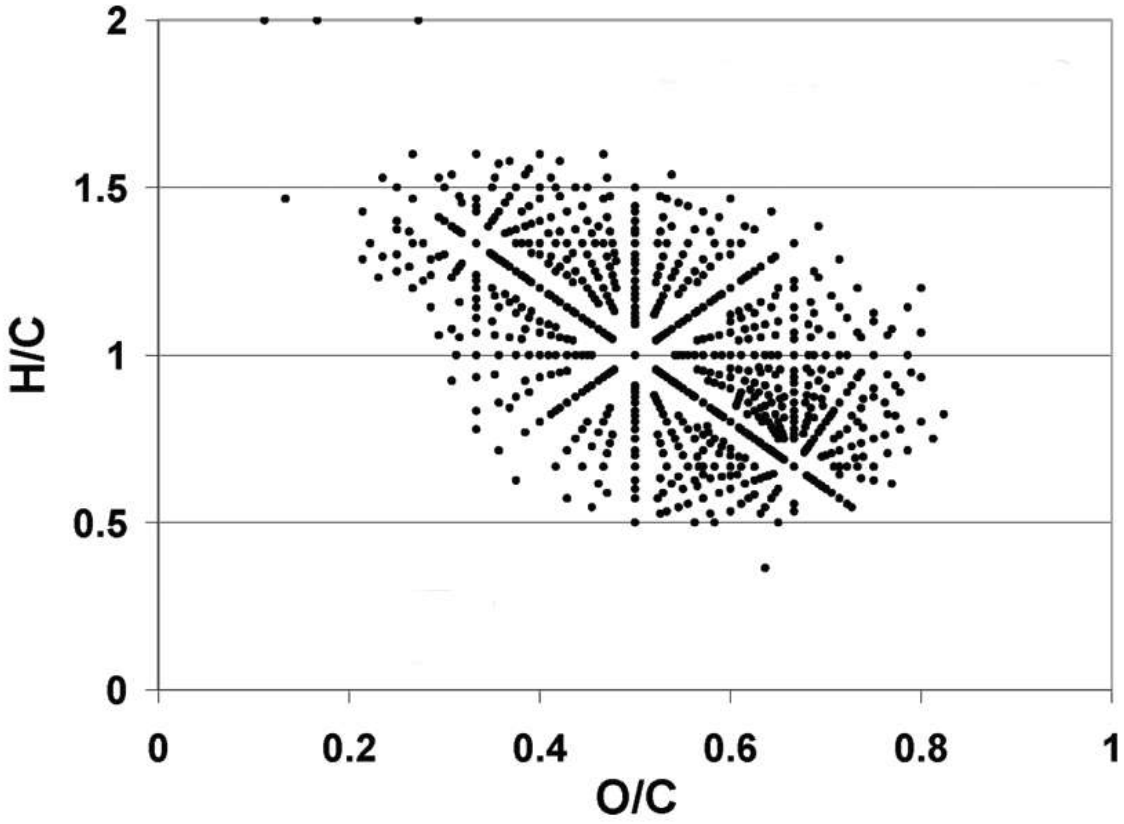

Figure 5. A relatively simple example of a van Krevelen plot. A prerequisite for such a plot is the availability of unambiguous elemental compositions for all peaks in the mass spectrum. Every single dot represents a mass measurement. In this example, the position of the dots is determined by the oxygen-to-carbon ratio in the elemental composition on the horizontal axis and the hydrogen-to-carbon ratio on the vertical axis. Chemically related compounds form regions or lines in these plots, and samples from different sources may, for example, be differentiated at a glance based on different relative oxygen content. Image from [Herzsprung, 2012]

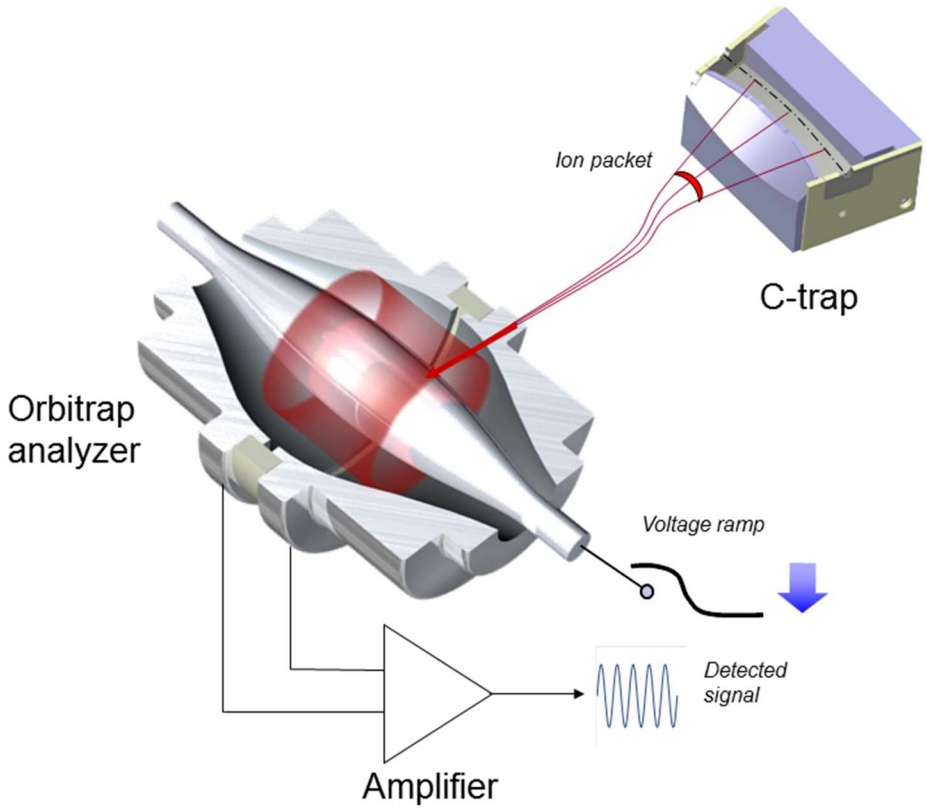

Figure 6. Scheme of the C-trap ion accumulation device and the Orbitrap mass analyzer with an example of an ion trajectory. A voltage ramp confines ion packets within the analyzer; the ion packets subsequently form oscillating rings that induce a current detected by the amplifier (reprinted with permission of Thermo Fisher Scientific, CCL2012).

Figure 7. Cut-outs of a standard (top) and a high-field (bottom) Orbitrap analyzer (reprinted with permission of Thermo Fisher Scientific, CCL2012).