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Milestones in Fourier transform ion cyclotron resonance mass spectrometry technique development

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Abstract

The present range and power of Fourier transform ion cyclotron resonance mass spectrometry rest on a number of prior technique developments. In this article, selected developments in neutral/ion introduction, ionization methods, excitation/detection, ion trap configuration/operating modes, ion dissociation and MS/MS, ion cooling techniques, theory and data reduction are briefly explained and chronicled. Evidence for the value of these techniques is provided by a compilation of current world records for mass resolution, mass resolving power and mass accuracy. With these capabilities, it becomes possible to resolve and identify up to thousands of components of a complex mixture, often without prior wet chemical separation, thereby potentially changing the whole approach to dealing with chemical and biological complexity. (Int J Mass Spectrom 200 (2000) 331–356) © 2000 Elsevier Science B.V.

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1. Introduction

At this writing, at least 325 Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometers have been installed worldwide, representing a capital investment of more than $100M in 2000 USA dollars, and several times more than that in associated personnel and operating costs. The principal underlying justification for that huge (and continuing) investment is that FT-ICR MS offers 10–100 times higher mass resolution, mass resolving power, and mass accuracy than any other mass analysis technique. As noted below, those capabilities in turn are changing the way in which chemical and biological analyses are performed, often by eliminating wet chemical separation steps. In addition, the capability to trap mass-selected ions for extended periods in the presence of collision or reagent gas generates a wealth of fundamental thermochemical and kinetic parameters for formation, chemical reaction and dissociation of gas-phase ions.

FT-ICR MS has already been the sole or principal subject of three books, four journal special issues, and more than 65 review articles [listed through 1998 in Ref. 1] since its inception in 1973. For example, a recent comprehensive primer provides a full-range technical introduction to ion behavior in combined magnetic and electric fields [1]. Other reviews de-

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scribe the early historical development of FT-ICR MS [2–5]; Fourier transform aspects [6]; parallels to Fourier transform nuclear magnetic resonance (FT-NMR) [7]; and a host of other techniques and applications. In this article, in the retrospective spirit occasioned by the 200th volume of the *International Journal of Mass Spectrometry*, we review the origin and principles of various techniques that comprise the working library of FT-ICR mass spectrometry. Applications will be treated in another article in this volume.

Finally, as noted previously [1], the close conceptual relation between Penning (ICR) and Paul (quadrupole) ion traps is perhaps most evident from the 1989 Nobel Prize, which was shared by Dehmelt and Paul, the two most famous developers of the two techniques. Many trapped-ion techniques first introduced in FT-ICR have since been adapted to the Paul trap: for example, collision-induced dissociation of trapped ions [8], mass-selective ion ejection [9], frequency-sweep excitation [10], stored-waveform excitation/ejection [11–14], Fourier transform detection of an induced image current [15,16] and the interfacing of various ion sources to the mass analyzer.

2. Pre-FT ion cyclotron resonance developments

2.1. Cyclotron

ICR developments prior to the introduction of pulsed excitation with FT data reduction have been reviewed elsewhere [17], and only a few selected aspects will be listed here. The cyclotron principle of periodic excitation to accelerate an ion to large ion cyclotron radius dates from Lawrence and Livingston in the early 1930s [18].

2.2. Omegatron

Cyclotron motion was first adapted for mass spectrometry in approximately 1950, in the *omegatron*. In that device, the bipolar pulsed excitation of Lawrence's cyclotron was replaced by continuous resonant excitation at the ion cyclotron frequency, leading to a continuous Archimedes spiral trajectory, culminating in detection of the charge deposited on a small collector blade. A mass-to-charge ratio (m/z) spectrum was acquired by slowly scanning the field of an electromagnet to bring ions of different m/z into resonance. Although their device exhibited relatively low mass resolving power by later standards, the omegatron developers showed considerable prescience, for example, in noting that ICR mass resolving power is the same as ICR frequency resolving power and in their use of segmented electrodes to shim the radio frequency (rf) electric dipolar field to high linearity [19].

2.3. Ion cyclotron resonance

The next major innovation, introduced by Wobschall at Cornell [20] and developed by Llewellyn at Varian [21] and Baldeschwieler's group at Stanford [22] was to detect ion resonant power absorption, rather than to count ions on a collector plate. That development made the ion cyclotron resonance (ICR) experiment conceptually (and in many respects, instrumentally) homologous to nuclear magnetic resonance (NMR), and subsequent ICR development has borrowed heavily from prior NMR techniques [7]. The experiment was still performed at fixed rf frequency, by scanning the magnetic field, thereby limiting the mass resolving power to a few hundred.

What made ICR so useful chemically was its ability to identify ion–molecule reactions, and determine their kinetics, equilibria and energetics by selectively changing the energy or population of ions of one mass-to-charge ratio and observing the effect on ions of the same or other mass-to-charge ratios, in an experiment introduced as ICR double resonance [23] and now known more generally as tandem mass spectrometry (or MS/MS). However, the experiment was still conducted at fixed rf excitation/detection frequency by varying the applied magnetic field strength, and it took about 30 min to acquire a spectrum from $16 \leq m/z \leq 200$, at a mass resolution of $\sim$1 Da.

Although FT-NMR was introduced by Ernst in

1966 [24], it still took another 7 years before FT-ICR mass spectrometry was realized. Some of the reasons should become evident as we now track the various elements of the FT-ICR MS experiment.

2.4. Single ion detection

Before proceeding to FT-ICR MS, we should stop to note that the highest-precision ICR-based mass measurements (to sub-ppb level) are typically performed on a single ion (initially, on a single electron [25]). Ion axial oscillation (see below) is detected by a superconducting quantum interference device (SQUID). Ions are then pulsed from axial to cyclotron mode for a precisely known period of time, and then back to axial mode for detection. The shift in axial oscillation phase for a series of such experiments performed at incremented cyclotron residence periods then provides a point-by-point cyclotron oscillation sinusoid from which the ICR frequency may be determined to extraordinary precision. Such experiments have been used for ultraprecise atomic mass measurements [26], and to determine the (lack of) mass difference between the proton and antiproton [27]. However, because such experiments require liquid helium temperature, and report only a single *m/z* value at a time, they are not applicable to analytical mass spectrometry in which a wide range of *m/z* values must be covered quickly.

3. Ionization methods

FT-ICR mass analysis begins with ionization of the species of interest. Table 1 chronicles various ionization methods coupled to FT-ICR mass spectrometry. Ionization may be performed at or adjacent to the ICR ion trap (internal ionization) or outside the main field of the magnet (external ionization). Internal ionization is convenient for volatile neutrals that may be leaked into the trap and then ionized by a beam of electrons (typically 70 eV, ~1 μA) or photons [28, 29] directed along the central axis of the ion trap. Chemical ionization [30] is also conveniently performed inside the ICR ion trap. Alternatively, low-volatility species may be deposited on a solids probe that is then brought close to the end cap of the ion trap, and either heated to vaporize the sample for EI, or a beam of photons or ions is aimed at the deposited sample to produce desorption/ionization. Internal ionization has several advantages: (a) Ions can be trapped with high efficiency, because the magnetic field focuses them to avoid ion loss in directions transverse to the magnetic field, and because ions need not traverse the fringe field of the magnet to enter the trap. (b) There is less time-of-flight *m/z* discrimination, because ions travel only a short distance before reaching the trap, so that differences in ion initial axial velocity are less important. (c) Ions are formed on or very close to the central symmetry axis of the trap, minimizing ion loss by magnetron orbit expansion [31]. As seen in Table 1, internal electron ionization was implemented well ahead of all other ionization methods and accounted for a large body of early fundamental determinations of ion–molecule reaction pathways, kinetics, and energetics to reveal ion identity, structure and bonding [32–37].

Table 1
Ionization methods coupled with FT-ICR mass spectrometry

Year	Ionization Method	Reference
1974	Electron ionization	[38]
1981	Self-chemical ionization	[30]
1984	Cs^+ fast ion beam	[39]
1984	Laser desorption/ionization	[40–42]
1985	Photoionization	[28,29]
1986	^{252}Cf plasma desorption	[43]
1988	Field desorption	[44]
1990	Fast atom bombardment	[45]
1989	Electrospray	[46–48]
1986	Cluster ions	[40]
1990	Cs^+ liquid SIMS	[50]
1990	High-pressure EI	[51,52]
1990	Laser desorption/EI	[53]
1990	Metal vapor vacuum arc	[54]
1991	Continuous-flow FAB	[55]
1991	Fast neutral beam	[56]
1991	MALDI	[57,58]
1993	Glow discharge (d.c.)	[59]
1996	Nano-ESI	[60]
1998	Micro-ESI	[61]

With the exception of electron ionization and chemical ionization, most ionization sources for FT-

ICR MS are now placed external to the magnet for one very simple reason. Provided that ions can somehow be guided through the fringe field to reach the ion trap (see Section 4) an existing commercial external ion source can usually be installed with minimal modifications (e.g., magnetic components can be used). Moreover, for the various desorption/ionization techniques, there is no need for a long (typically >1 m) retractable probe. Finally, for intrinsically high-pressure (>1 Torr) ion sources (notably electrospray, cluster sources, high-pressure sources), external placement of the ion source facilitates introduction of multiple stages of differential pumping to ensure the desired $<10^{-8}$ Torr pressure in the ICR ion trap. External ionization has been the preferred implementation for generation of ions from low-volatility analytes, such as metals, metal complexes and clusters, peptides, proteins, lipids, oligosaccharides, nucleic acids, synthetic polymers and noncovalent adducts with sufficiently strong ($>10^6$ M^{-1}) binding constants to survive, for example, electrospray ionization.

4. Neutral/ion introduction

The choice of how to introduce the sample and/or how to inject ions into the Penning trap depends on the choice of commercial (or homebuilt) instrument and on the sample composition, as chronicled in Table 2. For example, analysis of volatile hydrocarbon mixtures requires an all-glass heated inlet, to vaporize all of the sample components and keep them away from metal surfaces (to avoid pyrolysis) during sample introduction [62–64]. A pulsed valve is typically used to admit gas for ion-neutral collisions or reactions. Collisions can serve either to cool ions (see Section 8) or to heat ions internally to dissociate them into fragments (see Section 7). In either case, it is desirable to pump away the gas before ICR excitation/detection [65]. Placement of pulsed valves at both ends of a gas storage reservoir provides a particularly attractive means for leaking gas into the chamber at a well-controlled rate [66]. Concentric vacuum chambers [67] allow for differential pumping inside the bore of a superconducting magnet (for higher transmission efficiency of ions from one pumping stage to the next), but at the cost of increased construction complexity and reduced pumping efficiency (due to reduced cross-sectional area at each stage).

Table 2
Methods for introduction of neutrals or ions to a Penning trap

Year	Neutral/Ion Introduction	Reference
1974	Batch inlet	[38]
1981	Solids probe	[a]
1982	Gas chromatography	[82]
1983	Pulsed valve	[65]
1985	Multipole ion guide	[73]
1986	Supersonic jet	[49,72]
1986	Einzel lenses	[83]
1987	Supercritical fluid chromatography	[84]
1991	Liquid chromatography	[85,86]
1992	Concentric vacuum chambers	[67]
1993	Electrostatic (central wire)	[74]
1993	Capillary electrophoresis	[87]
1994	All-glass heated inlet	[62]
1994	Ext'l accum'n by QE	[70]
1996	Pulsed leak valve	[66]
1996	Stacked rings	[75]
1997	External ion accumulation	[77]
1999	Mass-selective ion injection	[78,79]
2000	Ion funnel	[76]

[a] Nicolet FTMS-1000 instrument.

For externally generated ions, the requirement that $\nabla \cdot B = 0$ means that off-axis ions will be subjected to a retarding force (magnetic mirror effect [68, 69]) in proceeding toward the center of a solenoidal magnet. The two ways to overcome the magnetic mirror effect are either to hold the ions close to the solenoidal magnet central axis during ion injection (because the magnetic mirror force is zero on-axis), or to accelerate the ions to sufficiently high speed that they pass through the potential energy barrier. The problem with accelerating ions through the magnet fringe field is that it becomes necessary to slow them down for capture in the Penning trap. If ions are produced during a short pulse, then the front trap potential may be gated open and shut to allow them in but not back out [49]. However, if ions are produced continuously, then they must be cooled during injection by collisions with buffer gas, preferably accompanied by azimuthal quadrupolar excitation [70] or side-kick excitation (see Section 8) by passing near a charged electrode that deflects the ion laterally and thereby converts some of its axial translational energy into cyclotron and magnetron energy [71].

Ions may be held on-axis by entrainment in a supersonic jet [49,72], or by radial confinement in an rf multipole ion guide [73], charged wire ion guide [74], or stacked-ring ion guide [75] or ion funnel [76]. The effective radial trapping potential in quadrupole, hexapole, octapole, stacked-ring and wire ion guides varies as $(r/r_{0)})^2$, $(r/r_{0)})^3$, $(r/r_{0)})^4$, $\exp(r/r_{0)}$ and $\log(r/R)$, in which r is the radial distance of the ion from the central axis of the guide, r_0 is the distance from the central axis of the guide to the nearest outer multipole electrode surface and R is the radius of the wire guide outer cylinder. The octapole offers the flattest near-axis radial potential, and can thus accommodate high ion density; the octapole also operates at lower rf voltage (~100 V) than the corresponding hexapole or quadrupole [77,78] However, the quadrupole offers the highest selectivity, if m/z-selective injection is desired [79]. The various ion guides work well enough that many ionization techniques that could be performed inside the magnet are often now performed externally [80,81].

5. ICR ion trap designs/modes

Ion trapping in FT-ICR MS is necessary for two reasons: First, ions must be confined for thousands or millions of ion cyclotron rotations in order that ICR frequency (and thence m/z) may be determined precisely. Second, trapped ions may be subjected to dissociation and/or chemical reaction, and the ionic products of those processes remain trapped for further analysis (e.g., MS/MS). The principles and operating modes of various ICR ion traps were reviewed comprehensively in 1995 [88], and advances related to FT-ICR MS are summarized in Table 3.

Table 3
ICR ion trap designs and operating modes

Year	ICR Ion Trap Designs/Modes	Reference
1970	Trapped-ion cell (pre-FT)	[91]
1974	Orthorhombic	[38]
1976	Closed cylindrical	[93,94]
1978	Electron beam ion trapping	[101]
1981	Cubic	[92]
1989	Multiple electrode pairs	[120,121]
1986	Dual cell	[95]
1987	Hyperbolic trap	[99]
1989	Screened trap	[122]
1989	Multiple electrode pairs	[120,121]
1989	Open cylindrical	[96,97]
1990	rf-shimmed side plates	[19,108–110]
1990	Harmonics-enhanced trap	[121,123]
1990	Compensated trap	[112,113]
1991	Infinity trap	[111]
1992	Capacitive coupling	[98]
1992	Combined trap	[105,107]
1993	Nested trap	[124]
1993	*xz* trap	[117]
1993	Segmented rings	[114]
1994	Kingdon trap	[102]
1994	Two-electrode trap	[100]
1995	Filar electrode trap	[116]
1997	Combined linear trap	[125]
1999	Matrix-shimmed trap	[115]

Briefly, an ICR ion trap is a volume enclosed by conductive electrodes, representing two types of compromises: (a) production of a three-dimensional axial quadrupolar electrostatic potential to confine ions in the magnetic field direction (z-axis), while also producing one-dimensional dipolar and/or two-dimensional azimuthal quadrupolar rf electric voltage in the x–y plane to excite one or more of the three natural ion motions (cyclotron rotation, magnetron rotation, and axial oscillation); and (b) the need to truncate the dimensions of the trap to fit into the available space, and to provide apertures to admit ions, neutrals, and photons for various experiments. The three-dimensional axial quadrupolar potential (“Penning” trap potential) is the only one for which the ion cyclotron resonance frequency is independent of ion location within the trap, thus minimizing inhomogeneous line broadening due to superposition of ion cyclotron resonances of different frequency for ions of the same m/z and eliminating mixing of ICR natural (normal) motional modes. Pure rf dipolar excitation is needed for linear ion behavior: namely, the ICR radius for a packet of ions of a given m/z is directly related to the excitation voltage amplitude:duration product, and the detected ICR signal is directly related to the ion packet radius. Only for such a linear system will the

Fourier transform of the time-domain ICR signal represent the true frequency-domain ICR spectrum (from which the *m/z* spectrum is then obtained, see Section 9).

Generation of a perfect three-dimensional axial quadrupolar dc potential (or perfect one-dimensional dipolar or two-dimensional axial quadrupolar potentials) would require infinitely extended charged conductive hyperbolic (or planar) electrodes. Very fortunately, it turns out that applying the same dc voltage to each axial end cap of just about any trap geometry will produce a perfectly quadrupolar electrostatic trapping potential at the trap center [88]. Thus, it is desirable to cool ions (see Section 8) to focus them near the center of the trap before ICR excitation/detection. Similarly, rf dipolar and quadrupolar potentials are near-perfect near the center of just about any trap. Equally fortunately, the distortions produced by introduction of spaces or apertures in the electrodes of the trap become negligible at locations more than a couple of dimensions of those spaces or apertures. As if all that weren't lucky enough, the natural ion motions themselves tend to average out spatial imperfections in the dc and rf electric potentials (except for radial spatial inhomogeneity in the magnetic field), because the difference in ion cyclotron frequency between different ion locations in the trap is small compared to the cyclotron frequency itself. This averaging effect, much like spinning the sample in nuclear magnetic resonance [89,90], further enhances ICR performance.

The need to trap ions for ICR experiments was understood and realized [91] even before the advent of the first Fourier transform ICR experiment. FT-ICR MS was performed initially with an orthorhombic trap [38], and with cubic [92] or closed-end cylindrical [93,94] traps for the next fifteen years or so. During that period, a particularly useful innovation was the dual trap [95], consisting of two adjoining traps separated by a vacuum conductance limit (i.e., a plate with a small hole in the center to allow passage of ions while maintaining a 100-fold pressure difference between the two ICR cells). The dual cell thereby effectively removed one pumping stage between the ion source ($>10^{-5}$ Torr) and the ICR cell ($<10^{-8}$ Torr). The most common trap configuration in use today is the open cylindrical trap [96,97], in which the flat end caps are replaced by cylinders to which a common dc voltage is applied. The open cylindrical trap has two advantages: (a) ions may enter off-axis, for greater potential efficiency of capture of an externally generated beam of ions; and (b) capacitive coupling (see Section 6) between the central and end cap cylinders effectively linearizes the dipolar rf excitation and detection potentials in the central trap section [98].

Literally dozens of other trap designs have been proposed and/or tested. For example, a truncated hyperbolic trap with either three [99] or two [100] electrodes produces a near-perfect three-dimensional axial quadrupolar trapping potential, but its curved sides are not optimal for dipolar rf excitation. A screened cubic trap, in which a fine-mesh grounded screen is inserted between each end cap and the central cell plates, produces a near-perfect particle-in-a-box potential, which is optimal for reducing space-charge effects (see Section 10) but spreads ions axially for nonoptimal excitation and detection linearity. Alternatively, ions may be trapped by a central line of charge, produced either by electrons [101] or by a charged wire [102].

A particular special case arises when it is necessary to trap both positive and negative ions simultaneously. One solution is a nested trap, in which an additional pair of end caps is added outside the usual end caps. Applying oppositely charged dc potentials to the inner and outer end caps allows for trapping of ions of one sign in the central compartment, and trapping of ions of the opposite charge sign in the adjoining outer compartments. The dc potentials (and/or ion axial kinetic energy) are adjusted so that ions of both charge signs spend at least part of their time in the same compartment. Although the axial spatial distributions of species of opposite charge signs are not the same, the nested trap has the advantage that electrons and molecular ions may both be trapped simultaneously. A second solution is the combined trap, in which (as in the Paul [103] or quadrupole [104] ion trap), an rf voltage is applied between the two end caps. Ions are thus confined radially by the combined effects of the applied magnetic field and the applied axial rf electric potential). Ions of both charge signs can be confined in such a trap [105, 106], but imposition of the rf voltage limits the available *m/z* range [107].

By segmenting the electrodes of an ICR ion trap, and applying an appropriate potential to each segment, it is possible to approximate more closely the potentials of any or all three types: three-dimensional axial quadrupolar electrostatic trapping potential, and dipolar and two-dimensional azimuthal quadrupolar rf electric potential. For example, cutting the side plates of a cubic trap into equally spaced segments, and applying a linearly divided voltage to each segment (as initially suggested by the omegatron designers back in 1951 [19]) generates near-perfect dipolar rf excitation [108, 109], as evidenced by virtually complete suppression of harmonics [110] and absence of *z*-ejection [108]. Similar improvement in rf dipolar potential linearity may be achieved either by segmenting the (flat) end caps of a closed cylindrical trap to simulate the potential of an infinitely extended cylinder (infinity trap [111]) or by capacitively coupling the segments of an open cylindrical trap [98]. Similarly, the electrostatic trapping potential may be improved somewhat by segmenting the flat circular end caps of a closed cylindrical trap [112, 113]. Finally, an axial quadrupolar trapping potential may be achieved in three ways [114]:

1. By applying a uniform potential to a conductive surface defined by $r_0^2 - 2z_0^2$ (i.e., the familiar hyperbolic-shaped trap).
2. By applying a potential varying as z^2 to a series of equal-radius rings.
3. By applying a voltage that varies linearly with z to a series of rings whose radii vary linearly with z.

However, the ultimate improvement to trap shimming is to cut each side of a cubic trap into multiple segments and apply appropriate voltages (obtained from the projections of each perfect potential field onto each trap plate) to each electrode segment, to produce the matrix-shimmed trap [115]. The matrix-shimmed design promises simultaneously near-perfect potentials of all three types while maintaining the symmetry and compact shape of a cubic Penning trap. Although in practice the added capacitance reduces the detection sensitivity of such a trap, it may still be worthwhile to shim for just two of the three potentials (e.g., dc trapping plus rf dipolar). For example, a trap constructed from filar electrodes [116] simultaneously optimizes dipolar and azimuthal quadrupolar rf excitations. Another example of segmentation is an *xz* cubic trap in which each end cap and one pair of opposed side plates is cut in half, so that appropriately applied rf voltages can couple ion axial and transverse (magnetron and/or cyclotron) motions [117]. Finally, segmentation of the side electrodes into 2^n opposed pairs of electrodes, and combining the signals from every second, fourth, eighth, etc. pair, can generate high-amplitude spectral response while suppressing the signal at the fundamental frequency, for potentially enhanced frequency separation between closely spaced resonances (see Section 10).

Although nonlinearity in ICR excitation and detection is generally to be avoided, harmonic signals can provide enhanced frequency separation between closely-spaced resonances, because the ICR motion is detected at harmonic (i.e., integer) multiples of the fundamental ICR frequency [118]. Although harmonic signals arise naturally during dipolar excitation in a typical cubic or cylindrical ion trap [119], their relative magnitude is typically a small fraction of that at the fundamental ICR frequency.

6. Excitation/detection

Excitation and (especially) detection define most clearly the transition from pre-FT to FT-ICR MS (see Table 4). In fact, the first FT-ICR experiment [38] simultaneously incorporated three advances that took place separately in the earlier parallel development of FT-NMR from its own non-FT precursor:

1. Magnetic field-sweep replaced by fixed magnetic field (thereby improving resolution from much higher spatial and temporal homogeneity in the magnet and from the spinning-the-sample effect

Table 4
ICR excitation and detection modes

Year	Excitation	Detection	Note	Reference
Pre-FT				
1949	CW dipolar	Simultaneous (charge collector)	a	[19,152,153]
1960	CW dipolar	Simultaneous CW	b	[20,21,126]
1971	CW dipolar	Simultaneous CW dipolar	c	[154]
FT-based				
1974	Pulsed dipolar	Delayed dipolar	d	[38]
1974	Frequency sweep dipolar	Delayed dipolar	e	[134]
1977	Frequency sweep dipolar	Simultaneous dipolar	f	[155]
1981	Dipolar	Single-plate	g	[156]
1984	Random noise	Delayed dipolar	h	[131]
1984	Pseudorandom noise	Delayed dipolar	i	[132]
1985	Stored waveform inverse Fourier transform	Delayed dipolar	j	[133]
1987	Dipolar	Analog quadrature heterodyne	k	[147]
1987	Parametric (ring)	Parametric (ring)	l	[139]
1988	Dipolar at 2× axial frequency		m	[140,141]
1989	Dipolar axial	Delayed dipolar axial	n	[157]
1989	Dipolar	Multipolar	o	[120,121]
1990	Dipolar	Axial quadrupolar	p	[158]
1990	Azimuthal quadrupolar		q	[136]
1990	Dipolar	Dipolar; Azimuthal quadrupolar	r	[150,151]
1991	Azimuthal quadrupolar with buffer gas (single *m/z*)		s	[137]
1991	Excite; 90° phase shift		t	[146]
1991	Multiple heterodyne	Multiple heterodyne	u	[159]
1992	Quadrature	Delayed dipolar	v	[106]
1992	Azimuthal quadrupolar with buffer gas (multiple *m/z*)			[138]
1993	Dipolar Magnetron	Delayed dipolar magnetron	w	[160,161]
1993	*xz* Dipolar	Delayed dipolar	x	[117]
1995	Azimuthal quadrupolar (2-plate)			[162,163]
1999	Dipolar	Digital quadrature heterodyne	y	[148]
2000	Azimuthal quadrupolar	Ion fluorescence	z	[164]

[a] Omegatron.

[b] Detection based on power absorption during excitation.

[c] Resotron—simultaneous excitation and detection on orthogonal pairs of plates, but one frequency at a time (not FT).

[d] FT-ICR MS, heterodyne detection of dipolar image current, orthogonal excitation/detection electrode pairs.

[e] Chirp excitation.

[f] Correlation ICR.

[g] Sideband detection.

[h] Incoherent time-domain acquisitions.

[i] Coherent time-domain acquisitions.

[j] SWIFT.

[k] Physical quadrature: simultaneous detection on orthogonal electrode pairs.

[l] Off-axis ions excited and detected with unbroken ring electrode.

[m] Axial ejection of electrons or ions by applying azimuthal dipolar excitation at twice the axial oscillation frequency.

[n] FT of axial oscillation image current.

[o] Suppression of fundamental ICR frequency in favor of harmonic multiples.

[p] Detect signal at unperturbed cyclotron frequency (independent of trapping potential).

[q] Cyclotron-to-magnetron mode interconversion (see also Ion Cooling Techniques).

[r] Ion remeasurement.

[s] Ion axialization by azimuthal quadrupolar excitation in the presence of collision buffer gas.

[t] Ion-lock: can effectively double or zero the applied static magnetic field.

[u] Detected frequencies of ions of two or more widely separated *m/z* values may be brought close together for high digital precision with relatively small data set size.

[v] Circularly polarized excitation (distinguish positive and negative ions).

[w] Generation and detection of coherent magnetron motion of initially off-axis ions.

[x] Couples axial motion with magnetron and cyclotron motions.

[y] Factor of $2^{1/2}$ improvement in signal-to-noise ratio.

[z] Directly detected fluorescence for Penning-trapped ions mass-selected by ICR.

[89] of cyclotron rotation at a fixed ICR orbital radius [90]).

2. Single excitation/detector electrode pair replaced by orthogonal excitation/detection electrode pairs.
3. Simultaneous excitation/detection based on power absorption [20,21,126] replaced by temporally separated excitation and detection based on image current [127] and analyzed by FT data reduction [6].

(Interestingly, orthogonal simultaneous excitation/detection (non-FT) was realized in 1971, 2 years before the first FT-ICR experiment, but Genequand's paper was in French and was overlooked by the English language ICR community.)

The principles and implementation of various FT-ICR excitation and detection modes have been extensively reviewed [1, 14, 128-130], according to their time-domain waveform type—single-frequency boxcar (impulse), frequency-sweep (chirp), noise [131,132], stored-waveform inverse Fourier transform (SWIFT) [14, 133]) and spatial symmetry (dipolar, quadrupolar, quadrature, parametric) and orientation (azimuthal, axial). By analogy to FT-NMR spectroscopy, the first time-domain excitation waveform for FT-ICR MS was a single-frequency pulse [38]. Shortly thereafter, a frequency-sweep waveform [134] was shown to offer much wider bandwidth at much lower maximum excitation voltage amplitude and much higher *m/z* selectivity at the borders of the excited *m/z* range; such chirp excitation remains in use today. The ultimately optimal ICR excitation waveform, SWIFT [14,133], is based on the high linearity of ICR excitation/response—thus, virtually any excitation amplitude–frequency profile may be generated by a time-domain waveform obtained by inverse Fourier transform of the desired excitation spectrum. SWIFT excitation has been extended with similar success to the quadrupole (Paul) ion trap as well [12,13,135].

Excitation and detection frequency, symmetry and direction determine which Penning-trapped ion motional mode(s) (cyclotron rotation, magnetron rotation and/or axial oscillation) will be stimulated or observed [129]. For example, azimuthal or axial dipolar irradiation excites pure cyclotron (or magnetron) or axial oscillation. Virtually all FT-ICR MS experiments today are based on azimuthal dipolar excitation on one pair of electrodes followed by azimuthal dipolar detection on an orthogonal pair of electrodes. Azimuthal quadrupolar excitation at the sum of the magnetron and cyclotron frequencies results in oscillatory interconversion between magnetron and cyclotron motion [136]. If collisional buffer gas is added, then the collisions reduce the cyclotron orbital radius and ions are axialized toward the central *z*-axis of the trap [137,138]. Parametric excitation [139] provides a way to stimulate cyclotron (and magnetron) motion without having to cut the side electrodes into segments. If the trapping potential is (as in any actual trap) not perfectly axial, three-dimensional quadrupolar, then axial and radial motions are coupled, and azimuthal dipolar excitation at twice the axial oscillation frequency will excite axial oscillation [140, 141]. This method has been used to eject electrons without having to excite them at their (inconveniently high) cyclotron frequency. Exploitation of other (mostly undesirable) nonlinearities in a Penning trap is described elsewhere [1,110,142–145]. Finally, an unusual effect follows by changing the (resonant) excitation phase by 90° after ions have reached their usual postexcitation orbit. The resulting ion-lock (analogous to spin-locking in NMR) produces an additional radial force that either reinforces or opposes the Lorentz force from the magnetic field, which is equivalent to suddenly increasing or decreasing (even to zero) the effective applied magnetic field [146].

It is intuitively obvious that the sense (clockwise vs. counterclockwise) of cyclotron rotation (and thus the charge sign of an ion) cannot be distinguished by dipolar excitation or detection. Usually, the point is moot, because the sign of the electrostatic trapping voltage determines that ions of only that charge sign will be trapped in the first place. However, with the advent of nested [124] or dynamic [105, 107] Penning traps (see Section 5), it is possible to trap ions of both charge signs simultaneously. Circularly polarized irradiation may be produced by applying sinusoidal voltages differing in phase by 90° to two pairs of orthogonal electrodes in so-called quadrature excitation [106]. Ions of a given charge sign will then respond to resonant (i.e., excitation at the ICR frequency for ions of that *m/z* value) circularly polarized excitation of the correct rotational sense. Alternatively, azimuthal dipolar irradiation (which excites ions of either charge sign) can be followed by charge-selective quadrature detection to select ions of just one charge sign [147]. Quadrature detection also offers an improvement by a factor of $2^{1/2}$ in signal-to-noise ratio [148].

The initial FT-ICR experiments were limited in both bandwidth and digital resolution by the choice of analog-to-digital (A/D) converter and thus were performed (as in FT-NMR) in heterodyne mode (i.e., mixing the ICR signal with that of a reference oscillator, then low-pass filtering to generate a spectral segment centered at the reference oscillator frequency) [93]. However, A/D performance has now improved to a level (20 Msamples/s, up to 23 bits/word, 4 Mword buffer memory) that even ultrahigh-resolution FT-ICR mass spectra may be acquired over a wide *m/z* range by direct-mode (i.e., sampling the detected ICR voltage signal directly). The ultimate mass resolving power (see Section 12 for examples) is achieved by digital quadrature heterodyne detection [148], in which the time-domain signal is sampled continuously, while at the same time being multiplied by discrete cosine and sine reference waveforms, with the resultants treated as mathematically complex data. Real-time digital filtering ensures that the filter bandwidth matches the Nyquist bandwidth (i.e., the frequency range determined by the sampling frequency).

FT-ICR detection is based on the image current induced by repeated cycling of an ion packet past the detection electrodes [92]. Detection sensitivity is thus limited to ~100 charges at room temperature for a 1-s data acquisition [149]. However, unlike other mass analyzers, FT-ICR detection is nondestructive. Summing N repeated data sets can thus potentially improve the signal-to-noise ratio of the cumulative data by a factor of $N^{1/2}$. Ion remeasurement was first achieved by allowing collisions to relax the ion cyclotron postexcitation orbital radius back to near-zero before the next excitation/detection cycle [150]. Much more efficient (and faster) remeasurement was later performed by quadrupolar axialization to collapse the postexcitation ion cyclotron orbital radius to near-zero between acquisitions [151].

7. Ion dissociation and MS/MS

The direct analytical impact of FT-ICR MS devolves mainly from its high mass resolution, resolving power, and accuracy (see Section 12). However, its impact on ion-molecule chemistry and biochemistry develops in large part from the ability to trap (and, if desired, *m/z*-select) precursor ions for reactive or nonreactive collisions with neutrals (see Table 5). Product ions of all *m/z* ratios remain trapped (unlike a quadrupole ion trap, in which ions of *m/z* less than ~1/3 of the precursor *m/z* value are generally not observed) and can then be observed at high resolution. The general principle of MS/MS was first introduced in (pre-FT) ICR as ICR double resonance [23] (by analogy to NMR double-resonance), in which ions of a given *m/z* value were cyclotron-excited to higher speed, and their ion-molecule reaction products monitored. FT-ICR made it possible to perform the same experiment much faster (by simultaneously observing product ions of all *m/z* values from a given precursor *m/z* [165], rather than observing a single product ion *m/z* while scanning one precursor *m/z* at a time) and with much higher *m/z* resolution and resolving power. Applications of tandem FT-ICR MS to high-mass biomolecules have recently been reviewed [166].

Collision-induced dissociation (CID, also known as collision-activated dissociation, CAD) of precursor ions in Paul or Penning ion traps is typically achieved by multiple ion-neutral collisions at relatively low ion lab-frame collision energy (10s to 100s of eV), rather than a single collision at several keV in typical ion-beam mass analyzers [167]. In ICR CID, ion internal energy thus builds up, stepwise with each collision, faster than it is lost, for example, by infrared emission from vibrational relaxation, until the ion fragments by unimolecular dissociation [168]. Although it is possible to accelerate ions continuously (by on-resonance excitation) to produce CID [169], it is generally preferable to limit the ion maximum kinetic energy by repeatedly accelerating and decelerating ions in one of three ways, each of which periodically modulates the ICR orbital radius (and thus the ion cyclotron kinetic energy) [1]:

1. Sustained off-resonant excitation (SORI) [170].
2. Multiple excitation collisional activation (MECA) [171], in which ions are periodically excited on-resonance, and their cyclotron motion is then allowed to relax by multiple collisions before the next excitation.
3. Very low-energy excitation (VLE) [172], in which ions are alternately excited and de-excited [173] by periodic 180° alternation in excitation phase.

Surface-induced dissociation (SID) has the advantage that potentially all of the lab-frame ion kinetic energy may be deposited into internal energy on collision. However, early attempts at SID were conducted within the Penning trap, thereby limiting the maximum ion kinetic energy available by accelerating the ion from one end of the trap to hit the end cap at the other end [174,175]. More recently, the SID experiment has been performed much more efficiently with ions generated outside the magnet and then accelerated to strike the far end cap of a Penning trap [176]. Typically, surface-induced dissociation efficiency to produce useful fragments occurs only over a narrow range of initial ion kinetic energy.

Ultraviolet photodissociation [40,177] and infrared multiphoton dissociation (IRMPD) [178–180] offer an *m/z*-independent means for heating ions until they dissociate. Since the center-of-mass energy available for collisional excitation varies approximately inversely with *m/z* for collisions of heavy ions with light neutrals, IRMPD thus becomes increasingly attractive for fragmenting large (e.g., biologically interesting) ions. Another advantage of photodissociation is that no gas need be introduced (and then pumped away). Apart from its analytical utility, time-resolved photodissociation kinetics affords other fundamental insights [181].

A particularly useful special limit is when ions that are thermally heated (i.e., exhibit a Boltzmann distribution in internal energy) dissociate at a rate sufficiently slow that the Boltzmann distribution is not significantly distorted. If, in addition, the ion contains more than ~50 atoms, then the Arrhenius activation energy is a good measure of the energy dissociation threshold (rapid energy exchange, REX, limit). In this limit (typically satisfied by ions containing more than ~50 atoms), ions at thermal equilibrium (temperature, T) with the blackbody radiation from the vacuum chamber will dissociate with a rate constant, k_d, from which the dissociation activation energy may be extracted from the slope of an Arrhenius-type plot of $\log(k_d)$ vs. $(1/T)$. This blackbody infrared radiative dissociation (BIRD) experiment [182–185] has proved especially useful for extracting activation energy for dissociation of biologically interesting noncovalent complexes (e.g., DNA duplexes). The same idea can be extended to other slow-heating methods, notably multiphoton infrared irradiation [186,187] and collisional slow heating [168], although one must then be careful to compare only relative dissociation energies, because one cannot be sure that two different ions (unless they are large and/or homologous in structure) will be heated to the same internal temperature at the same IR laser power (or collision energy and pressure).

A recent very promising method for dissociation of proteins is provided by capture of very low-energy (<1 eV) electrons. In electron capture dissociation (ECD), it is believed that the captured electron produces hydrogen atoms that then deposit internal energy locally at the site of cleavage, leading to characteristic fragmentation distributed very widely along the primary amino acid sequence [188,189]. Higher energy electrons can also fragment ions previously formed by electron impact [190].

8. Ion cooling techniques

As noted above, ICR behavior approaches idealized limits only if ions are located at or near the center of a Penning trap. Thus, it is desirable to cool ion translational motion, so that ions collect axially near the trap midplane. Moreover, ion radial position varies as $r = r_0 \exp(kt)$, in which r_0 is the ion initial

Table 5
Ion dissociation and tandem mass spectrometry (MS/MS)

Year	Ion Dissociation and MS/MS	Reference
1978	Double resonance	[23,165]
1978	Infrared multiphoton dissociation	[178–180]
1982	CID: on-resonance	[169]
1984	UV–visual photodissociation	[40,177,181]
1987	EIEIO	[190]
1990	Surface-induced dissociation	[174–176]
1991	CID: off-resonance (SORI)	[170]
1991	Infrared laser slow dissociation	[186,187]
1992	CID: on-resonance (VLE)	[172]
1993	CID: on-resonance (MECA)	[171]
1994	Blackbody infrared radiative dissociation	[182–185]
1998	Electron capture dissociation	[188,189]

magnetron radius and k is a constant directly related to the dc trapping potential and to neutral gas pressure. Therefore, it is also desirable to axialize ions so that their cyclotron orbits are centered on the trap z-axis.

Of course, externally injected ions must lose translational energy during one pass through the trap, or they will exit over the same potential barrier that they overcame in order to enter the trap. One method for reducing ion translational energy is to deflect ions laterally (side-kick) as they enter the trap [71]. The ion axial speed is reduced, by converting axial energy into cyclotron energy, with a cyclotron orbit tangent to the z-axis of the trap (i.e., large magnetron radius). Thus, the side-kick method succeeds in trapping externally injected ions, but at the cost of heating their cyclotron motion and displacing them off-axis (for reduced spatial coherence after subsequent dipolar excitation).

Methods for cooling ions translationally, developed mainly by plasma physicists working with atomic ions in Penning and Paul traps, may be classified as direct or sympathetic:

1. Buffer gas cooling—reduction in ion speed by nonreactive collisions of an ion with cold neutral gas atoms or molecules.
2. Evaporative cooling—lowering the trapping potential suddenly to a lower or zero value for a fixed period, and then restoring it, allowing the translationally hottest ions to escape.
3. Adiabatic cooling—slow reduction in trapping potential so that translationally hot ions escape while maintaining a monotonically decreasing Boltzmann temperature of the remaining ions.
4. Radiative cooling of electrons—loss in electron energy due to its angular acceleration during cyclotron motion.
5. Resistive cooling—dissipation of ion cyclotron or magnetron energy through the effective resistance of the detection circuit.
6. Laser cooling—absorption of photons from one direction and emission of photons in all directions.

In sympathetic cooling, self-cooled electrons or laser-cooled atomic ions cool polyatomic ions by mutual long-range Coulomb interactions.

Buffer gas cooling is by far the most common method for reducing ion axial speed, and features in most of the methods for trapping externally injected ions in Table 6. Buffer gas collisions also reduce the ion cyclotron radius [129]. However, buffer gas collisions lead to loss of ions by magnetron radius expansion [31]. Therefore, it is useful to add azimuthal quadrupolar excitation to convert magnetron motion into cyclotron motion [136], so that ion-neutral collisions collapse the cyclotron radius before cyclotron motion is re-converted into magnetron motion. The net effect is that ions are axialized; that is, the ion magnetron radius collapses to near-zero, and the cyclotron radius is also reduced to near-zero [137].

Evaporative cooling (also known as suspended trapping) has been used to limit the maximum number of trapped ions during GC FT-ICR MS, for improved mass accuracy [191]. Evaporative cooling also provides a means for determining the ion axial kinetic energy distribution to establish ion translational temperature [192]. Adiabatic cooling has been used to achieve the highest FT-ICR mass resolution at high mass, by lowering the trapping voltage to produce a very shallow trapping well with relatively few ions dispersed axially to minimize Coulomb repulsions [193]. Resistive cooling has been demonstrated [194] but is not generally useful because the ICR detection

Table 6
Ion and/or electron-cooling techniques. The years refer to the introduction of the method to FT-ICR MS

Year	Ion Cooling Techniques	Reference
	Collisional damping	(Most entries in Table 2)
1988	Evaporative cooling	[191,192]
1990	Side-kick translational cooling	[71]
1991	Resistive cooling	[194]
1994	Azimuthal quadrupolar axialization	[138]
1997	Electron self-cooling	[196]
1997	Sympathetic cooling of ions by electrons	[195]
1998	Adiabatic cooling	[193]

circuit is almost wholly capacitive at typical ICR frequencies [92,127]. Laser cooling (and its use for sympathetic cooling) has not been attempted in FT-ICR MS.

The rate constant for radiative cooling varies inversely with the square of ion mass [128] and is thus negligible except for electrons, whose cyclotron orbital radius damps exponentially with a time constant of ~1 s at a magnetic field of 3 T (and much faster at higher magnetic field) [195]. Once electrons have cooled themselves to the vacuum chamber temperature, then translationally hot negative ions can be cooled sympathetically by collisions with the cold electrons. Even though electrons have small mass, the Coulomb interaction is long range, and $\sim 10^6$ cold electrons can cool hot negative ions in a few seconds [195]. It is worth noting that sympathetic cooling by electrons cannot be achieved in a Paul trap, because it is not possible to trap electrons and negative ions simultaneously because their masses are too different.

9. ICR data processing

Digital data acquisition and processing has always been inherent to FT-ICR MS. Advances in the associated hardware are discussed in Section 11. Here, we consider advances in software as they relate to FT-ICR MS data reduction (Table 7). The first FT-ICR experiment established the basic event sequence of ion formation and pulsed rf excitation was followed by acquisition and analog-to-digital conversion to yield 2^n (where n is an integer) time-domain transient data (free ion decay), were followed by fast Fourier transformation (to yield mathematically real and imaginary spectra) and magnitude computation to yield a magnitude-mode frequency-domain spectrum [38]. About a decade later, a high-accuracy expression for frequency-to-*m/z* conversion took into account the cyclotron frequency shift due to application of a dc trapping potential [197].

Several aspects of FT-ICR data reduction derive directly from properties of Fourier transforms. For example, padding a time-domain data set with an equal number of zeroes (zero-filling) improves digital frequency resolution [198]. Time-domain (windowing) or frequency-domain (apodization) weighting of data enhances visual signal-to-noise ratio or analog resolution [6] but reduces the actual information content of the data. Fast Fourier transform (FFT) techniques can produce multiple frequency-derivative spectra with line shapes similar to those produced by apodization [199]. Surprisingly, it is possible to clip discrete time-domain data to as little as one bit per data point (i.e., just the sign of the signal) and still produce a recognizable FFT spectrum [200]. Oversampling can produce the same effect as increasing the dynamic range of the analog-to-digital conversion [201]. Many of the FFT manipulations applied to time-domain ICR data also apply to inverse FT manipulations for SWIFT excitation [202]. Foldover (aliasing) [6] reflects the apparent frequency of a FT spectral peak relative to the Nyquist frequency (i.e., half the sampling frequency). Thus, if the idea is high-resolution simultaneous detection of ions of widely separated *m/z* values, then undersampling can lead to multiple foldover to achieve high resolution, for example, for resolving N_2O^+ from $CO_2{}^+$, both at ~44 Da, while simultaneously resolving CO^+ from $N_2{}^+$ at *m/z* 28, without heterodyning) [203].

Phasing of FT-ICR data, namely, generating the appropriate linear combination of frequency-domain real and imaginary discrete spectra to yield absorption-mode and dispersion-mode is much more difficult in FT-ICR than for FT-infrared or FT-NMR spectroscopy, due to the wider typical FT-ICR frequency range (several decades). Thus, although phased absorption- and dispersion-mode spectra were produced almost immediately for ions of a single *m/z* [204], a phased broadband spectrum was not produced until 13 years later [205]. Absorption-mode display is desirable because it reduces the peak width at half-maximum height by a factor ranging from $3^{1/2}$ to 2 compared to magnitude-mode. Also, deconvolution to remove the nonuniform amplitude–frequency spectrum of any actual time-domain excitation waveform requires manipulation of mathematically complex (rather than magnitude-mode real) FT-ICR spectra [206].

Remarkably, a plot of the dispersion–absorption data (DISPA) yields a circle for a pure Lorentzian line shape [207]. The value of that result is that (a) spectral phase misadjustment is manifested as a rotation of the DISPA plot about its origin, and (b) deviations from circularity in such a plot afford a sensitive diagnostic for any of several non-Lorentzian peak shapes [208]. DISPA plots have been applied to FT-ICR data to aid in phasing to generate a pure absorption-mode spectrum [205] and to distinguish between hard-sphere and ion-induced dipole collision mechanisms [209].

The end goal of many FT-ICR data reduction schemes is to improve the precision and accuracy of *m/z* measurement. For example, one zero-fill before FFT improves precision by a factor of $2^{1/2}$, by combining the data originally residing separately as real and imaginary spectra; additional zero-fills do not improve precision, and in addition distort the spectral peak shape [210]. Interestingly, the precision improvement by zero-filling can be achieved alternately (without doubling the number of spectral data points) by use of the Hartley transform [211], which is equivalent to a Fourier transform but does not require mathematically complex data. Digital quadrature-detection (i.e., simultaneous acquisition of two heterodyne data sets differing by 90° in reference phase and treated as mathematically real and imaginary data) achieves a factor of $2^{1/2}$ improvement in signal-to-noise ratio (as well as twice the resolving power for a given frequency-domain bandwidth) [148]. Digital quadrature is distinct from physical quadrature (i.e., simultaneous detection from orthogonal pairs of electrodes [147, 212]), which realizes an additional $2^{1/2}$ signal-to-noise improvement.

Various interpolation and/or peak-fitting algorithms have been devised [213,214]. However, the ultimate precision in determination of, for example, peak position (from which *m/z* is derived) from a single discrete spectrum is proportional to the peak height-to-noise ratio and the square root of the number of points per peak width [215–217].

Fourier transformation is only one method for producing a frequency-domain spectrum from a discrete time-domain data set. Advantages of FT data reduction are the following: (a) The time-domain data are equally spaced, for simplified data acquisition; (b) there is a fast algorithm to perform the time-to-frequency conversion; and (c) the time-to-frequency conversion is determinative rather than iterative (i.e., one doesn't have to guess many answers and then iterate to find the best one). Various non-FT methods for converting time- to frequency-domain ICR data include linear prediction [218,219], maximum entropy [220–222], filtered diagonalization [223], and Hadamard transformation [224].

Two-dimensional ICR spectra potentially achieve the multichannel advantage in both stages of an MS/MS experiment. Basically, the idea is to modulate the number or energy of precursor ions of various *m/z* ratios, acquire a product ion spectrum, and then vary the precursor modulation pattern in a systematic way from one acquisition to the next, so as to be able to de-code the final data array. The experiment yields a two-dimensional spectrum whose projections identify all precursor-product pathways, as well as precursor-scan, product-scan, and neutral-loss scan spectra. Precursor modulation may be based on variable time delay (FT/FT) [225], SWIFT modulation (FT/FT) [226], or Hadamard encoding (Hadamard/FT) [224]. The applicability of two-dimensional ICR has to date been limited by the difficulty in finding a single set of conditions that will produce a comparable extent of fragmentation for a mixture of different precursors.

Several recent data-reduction tricks have been developed to deal with FT-ICR mass spectra of electrosprayed large molecules. The isotopic distribution for a protein of a given mass may be modeled

Table 7
FT-ICR data processing techniques

Year	FT-ICR Data Process	Reference
1973	FFT of free ion decay	[38]
1974	Phased spectrum for single *m/z*	[204]
1979	Zero-filling	[198]
1979	Deconvolved FT-ICR	[206]
1984	Frequency/mass calibration	[197]
1985	Clipped data	[200]
1986	Precision vs. S/N ratio and digital resolution	[215]
1986	Maximum entropy spectral computation	[220–222]
1987	Phased spectrum for range of *m/z*	[205]
1987	Dispersion vs. Absorption (DISPA)	[205,209]
1987	Interpolation of peak position	[213,214,216]
1987	SWIFT: digital aspects	[202]
1987	FT/FT 2D FT-ICR (variable time-delay modulation)	[225]
1988	Multiple foldover for resolution enhancement	[203]
1989	Hartley transform ICR	[211]
1990	Apodization (summary of several methods)	[6]
1990	Linear prediction spectral computation	[218,219]
1990	Oversampling	[201]
1990	Hadamard/FT 2D FT-ICR (Hadamard modulation)	[224]
1993	FT/FT 2D FT-ICR (SWIFT modulation)	[226]
1995	Magnitude-mode multiple derivative spectra	[199]
1995	Averagine for isotopic distribution computation	[227]
1995	Ion number from counting imprecision	[227]
1997	Deconvolution of natural isotopic distribution	[230]
1998	Deconvolution of charge state distribution	[228,229]
1999	Digital quadrature data reduction	[148]
1999	Filtered diagonalization spectral computation	[223]
2000	ESI internal calibration without standards	[231]

from *poly-averagine* (i.e., a protein whose composition is that of the average from a large protein database) [227], to facilitate molecular weight determination to within 1 Da. The information from multiple charge states of the same ion in an *m/z* spectrum may be deconvolved to yield a single mass-only spectrum [228,229]. It is also possible to deconvolve the natural-abundance isotopic distribution of a known peptide or protein [230], thereby facilitating interpretation of H/D exchange experiments. If multiple charge states of the same ion are present, then mass shifts for different charge states can provide for internal mass calibration without added mass standards [231]. Finally, because electrosprayed macromolecular ions typically possess multiple charges, it becomes possible to detect fluctuation in the number of such ions from one electrospray scan to the next. Since the root-mean-square fluctuation in ion number is simply the square root of the ion number, measurement of such fluctuation affords a direct measure of the number of those ions [227], without having to calibrate the detection electronics.

10. FT-ICR theory

For the present discussion, FT-ICR theory may be classified as follows: (a) ion trapping in static magnetic and electric fields; (b) ion trajectories and motional modes in static magnetic, static electric and rf electric fields; (c) generation and detection of an ICR signal; (d) spectral line shape; and (e) extraction of mass-to-charge ratio and mass from FT-ICR mass spectra (Table 8). Several aspects of each have already been discussed in preceding sections. Nonideality in each of the various applied fields has been treated in detail theoretically (Refs. 1,110,142−145 and references therein), but most nonlinearities (except as noted above) can be avoided experimentally.

10.1. Ion trapping

The Penning ion trap has been discussed in Section 5. In 1984, Ledford et al. [197] pointed out that there is an upper (critical) ion mass above which ions are no longer confined by the trap. Other, more restrictive upper mass limits follow from the requirements that the thermal ICR orbital radius be smaller than the distance between the trap side electrodes [1] and that the ion density be low enough to avoid coalescence of closely spaced resonances [232].

10.2. Ion trajectories.

Ion trajectories and motional modes are developed from idealized approximations. An ion of charge q (in C) and mass m (in kg) moving in a magnetic field B (in T) rotates at its unperturbed ion cyclotron frequency, $\omega_c = qB/m$. If the ion is initially at rest, application of an rf electric azimuthal (i.e., perpendicular to B) dipolar field at ω_c increases the ion cyclotron orbital radius linearly with time [129]. Resonant (or nonresonant) excitation of an ensemble of ions of different initial position and velocity is best visualized in a coordinate frame rotating at ω_c. In the rotating frame, the ion packet moves radially outward without changing its overall spatial distribution [233]. That spatial coherence is what makes FT-ICR detection possible. Off-resonant excitation [234] causes the ion cyclotron radius (and orbital speed) to oscillate between zero and a maximum value determined by the frequency offset from resonance and the amplitude of the rf electric excitation. Because ICR closely approximates a linear response system (see below), off-resonant excitation can equivalently be understood from the off-resonant response to resonant excitation [235]. Based on the linearity principle, the response-to-square-pulse [235], frequency-sweep [236], and SWIFT [133] excitation followed directly from the FT of their respective time-domain waveforms. In principle, linearity should make it possible to deconvolve the nonuniform excitation envelope from FT-ICR mass spectra [206], but it has not proved practical experimentally.

Two important principles greatly simplify the theoretical analysis of ion response to rf excitation in a Penning trap. First, if the magnetic field is spatially uniform, and the electrostatic trapping potential is purely axial three-dimensional quadrupolar, and the rf excitation potential is purely dipolar (i.e., spatially uniform rf electric field), then the ICR radius after a specified excitation period is proportional to the magnitude-mode spectral peak height of the excitation time-domain waveform at the ion cyclotron frequency [237]. This linearity principle means that the effect of any excitation waveform can be computed from its own Fourier transform spectrum, and one need not compute the ion trajectory to determine the postexcitation ion cyclotron radius. Second, the principle of reciprocity [238–240], also known as Earnshaw's theorem [241] applied to ICR states that the difference in charge, Δq, induced on two opposed trap side electrodes by a unit charge, $q(r)$, at position, r, and the electric potential $V(r)$ produced at that same point in space by applying potentials, V_0 and $-V_0$, to those same electrodes, are related by $\Delta q/q(r) = -V(r)/V_0$. Thus, it is never necessary to compute the induced charge directly, if one can solve the (computationally much simpler) problem of the potential field in a particular trap electrode configuration. Infinite series expressions are now available for computing the excitation potential [242,243] and induced charge response [240] for an ion anywhere inside a tetragonal or cylindrical Penning trap.

A particularly elegant theoretical framework for analyzing ICR excitation and detection is the v-vector approach of Brown and Gabrielse [128]. They analyze ion motions in an idealized Penning trap in terms of motional normal modes. Thus, ion motion is described as a linear combination of ion cyclotron, magnetron and axial motional amplitudes and frequencies. That model is especially efficient at describing the complex effects of azimuthal two-dimensional quadrupolar excitation (for axialization of off-axis ions) [130]. The same idea underlies Schweikhard's analysis of various excitation modes [129].

10.3. Generation and detection of an ICR signal

Generation of a spatially coherent ion packet and the charge induced on detector electrodes follows directly from the excitation theory and reciprocity principle outlined above. However, additional analysis is needed to compute the ICR signal current developed in an actual detection electronic circuit from the charge induced on opposed detector electrodes. The first model (whose qualitative features are preserved in more accurate subsequent approximations) was based on the charge induced on infinitely extended planar electrodes by a rotating monopole [92, 127, 244]. That model was later generalized and extended to more realistic trap configurations [149,243].

10.4. FT-ICR mass spectral peak shape.

FT-ICR mass spectral peak shape is theoretically simple in either of two limits: (a) zero pressure (i.e., no ion-neutral collisions), in which case the ICR time-domain signal evolves undamped, and frequency-domain peak sinc-function shape depends on the time-domain data acquisition period [235], and (b) high pressure (i.e., the time constant for ion-neutral collisions is much shorter than the time-domain data acquisition period), in which case the ICR time-domain signal damps exponentially to yield a frequency-domain Lorentzian line shape [245]. Line shape at intermediate pressure may be calculated analytically [245], leading to a quantitative analysis of the tradeoff between resolving power and signal-to-noise ratio [246]. Of course, in the zero-pressure limit, signal-to-noise and mass resolving power both increase at longer time-domain signal acquisition period [247].

Ion-neutral collisions in the preceding treatment were treated as Langevin's ion-induced dipole [234,248,249] model, in which ion-neutral collision rate constant is independent of pressure. Although the Langevin model is appropriate for room-temperature ions, a hard-sphere model is more appropriate for ions whose cyclotron radii have been excited to a radius of 1 cm (as in typical ICR detection). ICR line shape in the hard-sphere collision model is not analytic, but may be computed numerically [209]—the spectral peak is narrower near the center and broader in the wings than the corresponding Lorentzian.

Qualitative understanding of some of the effects of ion–ion Coulomb repulsion on FT-ICR mass spectral peak shape has been gained from analytical calculations [250,251], particularly with respect to coalescence of closely spaced resonances [232,252]. Also, some progress has been made by scaling ion behavior at high ion density and high magnetic field by putatively similar behavior at lower ion density and lower magnetic field [112]. However, it is likely that numerical computations will be necessary for realistic modeling of ICR behavior at high ion density.

10.5. Extraction of m/z and mass from FT-ICR mass spectra

The axial three-dimensional electrostatic trapping potential shifts the ion cyclotron resonance in a calculable way, leading to a highly accurate cyclotron frequency-to-*m/z* conversion formula [197] that remains in use today [253]. Methods for extracting mass-only spectra from *m/z* spectra were discussed in the previous section.

11. Infrastructure developments

Although not strictly scientific advances in themselves, several ongoing improvements in the hardware and software infrastructure of FT-ICR MS continue to contribute mightily to its increasing capability and popularity. Some important advances are collected below.

11.1. Magnets

The readily available magnetic field strength for FT-ICR MS has increased from ~1.4 T (resistive wire magnet) in the mid 1960s to 11.5 T (superconducting

Table 8
FT-ICR theory developments

Year	FT-ICR Theory (non-FT aspects)	Reference
1938	Excitation/detection reciprocity	[238–241]
1967	Off-resonant excitation	[170,234,235]
1976	Zero-pressure line shape for single-frequency excitation	[235]
1978	Detection circuit signal model	[92,127,149,243]
1979	Arbitrary-pressure line shape/single-frequency excitation	[245]
1980	Resolution vs. S/N ratio tradeoff	[246.247]
1980	Frequency-sweep excitation	[236]
1984	Frequency/mass calibration	[197,253,254]
1984	Upper mass limit (critical mass) due to trapping potential	[197,255]
1985	Stored-waveform inverse Fourier transform excitation	[133]
1986	*v*-vector formalism (cyclotron/magnetron normal modes)	[128–130]
1990	Rotating frame representation	[233]
1990	Potential field in tetragonal or cylindrical ion trap	[242,243]
1990	Scaling of ion behavior from low-field modeling	[112]
1991	Induced charge/ion in a tetragonal or cylindrical trap	[240]
1991	Excitation/detection lineaerity	[237]
1991	Ion-lock	[146]
1992	Space charge effects	[250,251]
1995	Coalescence of closely-spaced resonances	[232,252]
1998	Hard-sphere collision line shape	[209]

magnet) [256] and even 25 T (Florida-Bitter resistive plates magnet) [257] in 2000. The advantages of higher magnetic field for FT-ICR MS have been summarized elsewhere [258]. First, mass resolving power, $m/\Delta m_{50\%}$, in which m is ion mass and $\Delta m_{50\%}$ is FT-ICR mass spectral peak full width at half-maximum peak height, increases linearly with increasing applied magnetic field induction, B, for fixed ion-neutral collision frequency [235]. In fact, seven other FT-ICR primary performance parameters theoretically also increase linearly (data acquisition speed, upper mass limit for peak coalescence) or quadratically (upper mass limit due to trapping potential, maximum ion kinetic energy, maximum number of trapped ions, maximum ion trapping duration, two-dimensional FT-ICR mass resolving power) with increasing B [258]. These fundamental advantages in turn generate corollary improvement in other FT-ICR performance parameters: for example, signal-to-noise ratio, dynamic range, mass accuracy, ion remeasurement efficiency and mass selectivity for MS/MS. Moreover, modern superconducting magnets offer a bore inner diameter of 150–220 mm, thereby offering additional improvement in dynamic range because more ions can be accommodated without peak distortion or coalescence [232] of closely spaced resonances. Finally, these various advantages may be exploited in combination, so as to produce even higher enhancement in a particular parameter: for example, signal-to-noise ratio can improve by more than a factor of B^2 if mass resolving power is fixed at the same value as at lower magnetic field [259].

11.2. Digital data acquisition, storage, and manipulation

The first FT-ICR mass spectrum (December 17, 1973) was produced by FFT of 1 kWord time-domain data by a Varian 620L computer in a few seconds [38]. The Cooley-Tukey FFT algorithm computation time of an N-word data set ($N = 2^n$, in which n is an integer) scales as $N\log^2 N$ [260]. Thus, modern FFT computation of a 1 MWord time-domain data set in ~1 s [261] represents a ~10,000-fold speed improvement. Moreover, analog-to-digital converters have improved in speed (from ~50 ksamples/s up to ~20 Msamples/s), digital precision (from 8 bit/word to 23 bit/word) and storage capacity (8 Kword to 4 Mword stored data) [148]. Thus, even a very high-resolution FT-ICR mass spectrum may now be acquired in direct mode [6], thereby virtually eliminating the need for heterodyne mode detection (see below) except in very special cases.

11.3. Vacuum technology

For optimal performance, FT-ICR detection should be performed at a pressure sufficiently low (10^{-8}–10^{-9} Torr) that an ion undergoes (on the average) less than one collision [245] during an acquisition period of 1–10 s. Over the past 25 years, increasingly reliable means for routinely achieving such pressure have been provided by ion pumps, cryopumps and turbopumps.

12. FT-ICR mass precision, resolving power, and resolution records

As noted in Section 10, most of the fundamental aspects of FT-ICR MS may be understood from very simple idealized models [1]. Moreover, the effects of various nonlinearities in the applied magnetic and electric fields as well as space charge from the ions themselves may be treated as small perturbations (e.g., by Taylor series expansion, keeping only the lowest-order terms). What is most remarkable is how well the actual experiment works, given the number and degree of various perturbations. Perturbations include truncated (rather than infinitely extended) trap electrodes; perforated (rather than smooth) electrode surfaces; magnetic field spatial inhomogeneity; spatial misalignments; Coulomb repulsions between ions; distortion of the electrostatic trapping potential by the charge of the trapped ions themselves; imperfect spatial coherence of ion packet(s); and so on.

First, the primary basis for ultrahigh mass resolution (and mass resolving power and mass accuracy) in FT-ICR MS is the high temporal stability (typically to a few parts per billion per hour) of the magnetic field that confines the ions radially. Second, the natural motions (cyclotron rotation, magnetron rotation, and axial oscillation) of an ion in a Penning trap effectively time-average spatial inhomogeneity in the magnetic field and in the electrostatic trapping potential. Third, distortion of the electrostatic potential by ion space charge may be limited by reducing the number of ions and co-adding many successive detected scans and/or by operating at higher magnetic field strength. Fourth, Coulomb repulsion between ions of different *m/z* parked at the same cyclotron orbital radius is not critical, because as ions of one *m/z* approach ions of another *m/z*, the resulting $E \times B$ force pushes them apart as the ions pass each other, with essentially no net effect on their cyclotron frequencies.

Applications of FT-ICR MS to analytical, chemical, environmental and biological problems are discussed elsewhere in this volume and in prior recent reviews [64,262–270]. Applications addressed best by FT-ICR MS are those that benefit most by ultrahigh mass resolution, mass resolving power and mass accuracy. For example, complex mixtures ranging from crude oil to protein tryptic digests may often be analyzed without prior separation (GC, LC, CE, gels), for direct identification (elemental composition, amino acid composition/sequencing for protein identification, etc.). Even so-called targeted analysis, in which one seeks to find a known component, can benefit from high resolution, because impurities or interferants of very similar *m/z* may obscure the target at lower mass resolution.

This review concludes simply by listing various current world records for mass accuracy; mass resolving power, $m/\Delta m_{50\%}$ and mass resolution (defined here as the minimum mass difference at which two equal-height peaks may be baseline-resolved) Table 9. Although directly related, these three performance measures can differ, in practice, by more than an order of magnitude. First, mass accuracy can be much higher than the mass resolving power for the same peak, because it is possible to estimate the center of a peak to within much less than the peak width, provided that the signal-to-noise ratio and number of data points per peak width are sufficiently high [215]. Second, optimal mass resolution of two closely-spaced resonances can be much poorer than one would expect

Table 9
FT-ICR world records for mass analysis

Mass accuracy/elemental composition
1. Highest mass accuracy over wide mass range: ±0.5 ppm from 90–300 Da;[a] ±1 ppm from 250–1000 Da[b]
2. Highest mass for unique elemental composition: 895 Da[c]
3. Highest mass precision: ±0.000 000 09 Da @ 20 Da[d]

Mass resolving power, $m/\Delta m_{50\%}$
1. Highest resolving power for ions of a single *m/z*: 200,000,000[e]
2. Highest resolving power for ions of multiple *m/z* at high mass: 8,000,000 @ 8.6 kDa[f]

Mass resolution (separation of closely-spaced masses)
1. Highest resolution of two molecules: 0.00045 Da @ 906 Da[g]
2. Highest direct-mode (broadband resolution): 0.0034 Da @ 1326 Da[h]
3. Highest mass for resolved isotopic fine structure: 15.8 kDa[i]
4. Highest mass for unit mass resolution: 112 kDa[j]

Most complex mixture analyzed from a single mass spectrum
1. ~5,000 elemental compositions[k,l]
2. 583 peptides, resolved to better than 1 Da[m]

Highest mass for a chemically pure molecule: 100,000,000 Da[n]

Tandem mass spectrometry
1. Highest mass resolving power for MS^1: 20,000[o]
2. Highest mass resolving power for MS^2: Similar to FT-ICR without MS^1

[a] Electron-ionized diesel fuel (~500 elemental compositions in the stated mass range) [64].

[b] Electrosprayed petroleum heavy crude oil [274].

[c] The $^{13}C_{44}$ form of a 36:2 phosphatidylinositol (i.e., phosphatidylinositol in which the two alkyl side chains of the phospholipid total 36 carbons and two double bonds) for the all-^{13}C electrosprayed molecule [275].

[d] Electron-ionized ^{20}Ne [276]. This precision is the highest achieved by FT-ICR MS, in which ions of two or more *m/z* values are present simultaneously. Even higher precision has been achieved by trapping ions of just a single *m/z* value at a time, for which Fourier transform methods are not needed [26].

[e] Electron-ionized ^{40}Ar [277] and ^{3}He [278]. This performance is by FT-ICR MS. Higher resolving power for ions of a single *m/z* can be obtained by non-FT ICR techniques [26].

[f] Electrosprayed bovine ubiqutin [193].

[g] Two electrosprayed doubly protonated peptides, $(RVMRGMR+2H)^{2+}$ and $(RSHRGHR+2H)^{2+}$, of neutral monoisotopic mass, 904 Da [279]. The elemental compositions of these molecules differ by N_4O vs. S_2H_8, or ~0.00045 Da, namely, by less than one electron's mass (0.00055 Da)!

[h] Two electrosprayed peptides, $(ALANGMARSHALL+2H)^{2+}$ and $ALANGPARSHALF+2H)^{2+}$, of neutral monoisotopic mass, 1324 Da [279]. The elemental compositions of these molecules differ by C_3 vs. SH_4. The same elemental composition difference has also been resolved for electron-ionized molecules at 200–300 Da [64].

[i] Electrosprayed p16 tumor suppressor protein [193]. Isotopic fine structure (CH_4 versus O, differing by 0.036 Da) has also been resolved in glycidyl methacrylate/butyl methacrylate copolymers of up to 7 kDa [280].

[j] Electrosprayed chondroitinase [281].

[k] Electrosprayed petroleum heavy crude oil [274].

[l] Electrosprayed humic substances [282].

[m] Glu-C digest of a 191 kDa protein [266]. Although only 583 peptides are present, each can exhibit multiple charge states, and each charge state includes several isotopic peaks, for a total of several thousand peaks.

[n] A single DNA molecule, with ~30,000 charges [283].

[o] Stored waveform inverse Fourier transform (SWIFT) mass-selective ion ejection [284]. Limited by imperfection in the dc and rf electric potentials—potentially improveable by shimming of those potentials to near-ideal profiles [115].

from the maximum mass resolving power of a well-separated resonance, due to the tendency of two closely spaced resonances to coalesce [232,271,272].

With those considerations in mind, let us now turn to Table 9. It is not surprising to find that the performance records listed there were obtained with relatively high-field magnets (6–9.4 T). In the first place, ICR mass resolving power increases directly with increasing magnetic field, *B* [19,235]. Second, the tendency for closely spaced resonances to coalesce varies inversely with *B* [271, 273]. Third, ICR upper mass limit varies directly with *B* [1,197].

13. Conclusions

As this chronology demonstrates, the progress that has led to the present level and range of FT-ICR MS performance represents contributions in physics, engineering and computing, from a large number of scientists. During the 27 years since the first FT-ICR experiment, we have gained a much deeper understanding of the details of ion formation, injection, trapping, excitation, detection and data reduction. Although some key advantages (notably simultaneous high mass resolution over a wide mass range) were foreseen at the outset, the modern impact of FT-ICR MS also depends strongly on other developments that came much later (notably MALDI and electrospray ionization).

This review closes with some (always risky) forecasts of anticipated future directions for FT-ICR MS technology. At the high-performance end, the most obvious direction is toward ever-higher magnetic fields. Superconducting magnets up to 11.5 T [256] are already in use for ICR, with at least one 15 T system under development. FT-NMR superconducting magnets up to 21.1 T (900 MHz for 1 H NMR) systems exist. FT-ICR MS has been performed at 25 T with a Florida-Bitter resistive magnet [257], and even better performance can be anticipated from a hybrid magnet whose superconducting and resistive coils are connected in series (so that the high inductance of the superconducting magnet will limit temporal fluctuations in the low-inductance resistive coil). There are no technical barriers to such a hybrid magnet up to at least 27 T with 110 mm bore diameter.

Another magnet improvement may be to pump the helium dewar so as to lower the boiling point of liquid helium from ~4.2K to ~2K, thereby allowing more current to pass through the same superconducting coil. In this way, the upper limit for a NbTi-based coil may be increased from 9.4 to 11 T, thereby avoiding the need for more expensive (and fragile) Nb_3Sn conductor to reach that field. Yet another development is to cool a superconducting magnet by refrigeration (with helium as the working substance) rather than by cryogen boiloff, thereby eliminating the need for frequent and expensive replacement of liquid nitrogen and helium.

Finally, several companies are developing benchtop FT-ICR MS instruments based on a permanent magnet (0.6–1.0 T). Although their performance will obviously not compete with high-field FT-ICR MS instruments, their versatility and mass resolution should compare favorably with other alternative mass analyzers at the benchtop price range.

In conclusion, this review lists many milestones in FT-ICR MS development, because there has been a lot of mileage during the past 27 years! It seems safe to predict a bright future for this technique, because it offers 10–100 times higher mass resolving power than any other mass analyzer.

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References

[1] A.G. Marshall, C.L. Hendrickson, G.S. Jackson, Mass Spectrom. Rev. 17 (1998) 1.
[2] M.B. Comisarow, in A.G. Marshall (Ed.), Fourier, Hadamard, and Hilbert Transforms in Chemistry, Plenum, New York, 1982, p.125.
[3] A.G. Marshall, Acc. Chem. Res. 18 (1985) 316.
[4] M.B. Comisarow, A.G. Marshall, J. Mass Spectrom. 31 (1996) 581.
[5] A.G. Marshall, in D.M. Grant, R.K. Harris (Eds.), Encyclopedia of Nuclear Magnetic Resonance, Vol. 1, Wiley, London, 1996, 486.
[6] A.G. Marshall, F.R. Verdun, Fourier Transforms in NMR, Optical, and Mass Spectrometry: A User's Handbook, Elsevier, Amsterdam, 1990.
[7] A.G. Marshall, Acc. Chem. Res. 9 (1996) 307.
[8] J.N. Louris, J.S. Brodbelt-Lustig, R.G. Cooks, G.L. Glish, G.J. van Berkel, S.A. McLuckey, Int. J. Mass Spectrom. Ion Proc. 96 (1990) 117.
[9] D.E. Goeringer, W.B. Whitten, J.M. Ramsey, S.A. McLuckey, G.L. Glish, Anal. Chem. 64 (1992) 1434.
[10] S.A. McLuckey, D.E. Goeringer, G.L. Glish, J. Am. Soc. Mass Spectrom. 2 (1991) 11.

[11] M.H. Soni, R.G. Cooks, Anal. Chem. 66 (1994) 2488.

[12] R.K. Julian, Jr., R.G. Cooks, Anal. Chem. 65 (1993) 1827. [13] S. Guan, A.G. Marshall, Anal. Chem. 65 (1993) 1288.

[14] S. Guan, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 157/158 (1996) 5.

[15] J.E.P. Syka, W.J. Fies, Jr., U.S.A. Patent No. 4,755,670, 1988.

[16] M. Soni, V. Frankevich, M. Nappi, R.E. Santini, J.W. Amy, R.G. Cooks, Anal. Chem. 68 (1996) 3314.

[17] A.G. Marshall, in Z. Fisk, L. Gor'kov, D. Meltzer, R. Schrieffer (Eds.), Physical Phenomena at High Magnetic Fields, Vol. II, World Scientific Publishing Co, Singapore, 1996, 626.

[18] E.O. Lawrence, M.S. Livingston, Phys. Rev. 40 (1932) 19.

[19] H. Sommer, H.A. Thomas, J.A. Hipple, Phys. Rev. 82 (1951) 697.

[20] D. Wobschall, Rev. Sci. Instrum. 36 (1965) 466.

[21] P.M. Llewellyn, U.S.A. Patent No. 3,390,265, issued 25 June, 1969.

[22] J.D. Baldeschwieler, Science 159 (1968) 263.

[23] L.R. Anders, J.L. Beauchamp, R.C. Dunbar, J.D. Baldeschwieler, J. Chem. Phys. 45 (1966) 1062.

[24] R.R. Ernst, W.A. Anderson, Rev. Sci. Instrum. 37 (1966) 93.

[25] R.S. Van Dyck, Jr., P.B. Schwinberg, H.G. Dehmelt, Phys. Rev. D34 (1986) 722.

[26] F. DiFillip, V. Natarajan, M. Bradley, F. Palmer, D.E. Pritchard, Physica Scripta T59 (1995) 144.

[27] G. Gabrielse, X. Fei, L.A. Orozco, R.L. Tjoelker, J. Haas, H. Kalinowsky, T.A. Trainor, W. Kells, Phys. Rev. Lett. 65 (1990) 1317.

[28] M.P. Irion, W.D. Bowers, R.L. Hunter, F.S. Rowland, R.T. McIver, Chem. Phys. Lett. 93 (1982) 375.

[29] G.J. Carlin, B.S. Freiser, Anal. Chem. 55 (1983) 955.

[30] S. Ghaderi, P.S. Kulkarni, E.B. Ledford, Jr., C.L. Wilkins, M.L. Gross, Anal. Chem. 53 (1981) 428.

[31] S. Guan, Y. Huang, T. Xin, A.G. Marshall, Rapid Commun. Mass Spectrom. 10 (1996) 1855.

[32] M.L. Gross, D.L. Rempel, Science 226 (1984) 261.

[33] B.S. Freiser, in J.M. Farrar, W.H. Saunders, Jr. (Eds.), Techniques for the Study of Ion Molecule Reactions, Vol. 20, Wiley, New York, 1988, p. 61.

[34] B.S. Freiser, Chemtracts—Anal. Phys. Chem. 1 (1989) 65.

[35] N.M.M. Nibbering, Acc. Chem. Res. 23 (1990) 279.

[36] B. Asamoto, R.C. Dunbar, Analytical Applications of Fourier Transform Ion Cyclotron Resonance Mass Spectrometry, VCH, New York, 1991.

[37] K. Eller, H. Schwarz, Chem. Rev. 91 (1991) 1121.

[38] M.B. Comisarow, A.G. Marshall, Chem. Phys. Lett. 25 (1974) 282.

[39] M.E. Castro, D.H. Russell, Anal. Chem. 56 (1984) 578.

[40] W.D. Bowers, S.-S. Delbert, R.L. Hunter, R.T. McIver, Jr., J. Am. Chem. Soc.,106 (1984) 7288.

[41] B.S. Freiser, Talanta 32 (1985) 697.

[42] D.A. McCrery, M.L. Gross, Anal. Chim. Acta 178 (1985) 91.

[43] J.C. Tabet, J. Rapin, M. Porteti, T. Gaümann, Chimia 40 (1986) 169.

[44] I. Ipezsa, H. Knoll, K.-P. Wanczek, H.B. Linden, Proc. 36th Amer. Soc. Mass Spectrom. Conf. on Mass Spectrom. & Allied Topics, San Francisco, CA, 1988, p. 618.

[45] C.B. Lebrilla, D.T.-S. Wang, R.L. Hunter, R.T. McIver, Jr., Anal. Chem. 62 (1990) 878.

[46] K.D. Henry, E.R. Williams, B.-H. Wang, F.W. McLafferty, J. Shabanowitz, D.F. Hunt, Proc. Natl. Acad. Sci. USA 86 (1989) 9075.

[47] B.E. Winger, S.A. Hofstadler, J.E. Bruce, H.R. Udseth, R.D. Smith, J. Amer. Soc. Mass Spectrom. 4 (1993) 566.

[48] S.C. Beu, M.W. Senko, J.P. Quinn, F.W. McLafferty, J. Amer. Soc. Mass Spectrom. 4 (1993) 190.

[49] J.M. Alford, P.E. Williams, D.J. Trevor, R.E. Smalley, Int. J. Mass Spectrom. Ion Processes 72 (1986) 33.

[50] C.F. Ijames, C.L. Wilkins, J. Amer. Soc. Mass Spectrom. 1 (1990) 208.

[51] C.E.C.A. Hop, T.B. McMahon, G.D. Willett, Int. J. Mass Spectrom. Ion Processes 101 (1990) 191.

[52] P. Kofel, T.B. McMahon, Int. J. Mass Spectrom. Ion Processes 98 (1990) 1.

[53] D.M. Lubman (Ed.), Lasers in Mass Spectrometry, Oxford University Press, New York, 1990.

[54] B.H. Wang, I.J. Amster, F.W. McLafferty, I.B. Brown, Int. J. Mass Spectrom. Ion Processes 100 (1990) 51.

[55] C.H. Watson, G. Kruppa, J. Wronka, F.H. Laukien, Rapid Commun. Mass Spectrom. 5 (1991) 249.

[56] N.C. Hill, P.A. Limbach, R.E. Shomo, II, A.G. Marshall, A.D. Appelhans, J.E. Delmore, Rev. Sci. Instrum. 62 (1991) 2612.

[57] R.L. Hettich, M.V. Buchanan, Int. J. Mass Spectrom. Ion Processes 111 (1991) 365.

[58] J.A. Castoro, C. Köster, C. Wilkins, Rapid Commun. Mass Spectrom. 6 (1992) 239.

[59] C.H. Watson, J. Wronka, F.H. Laukien, C.M. Barshick, J.R. Eyler, Anal. Chem. 65 (1993) 2801.

[60] G.A. Valaskovic, N.K. Kelleher, F.W. McLafferty, Science 273 (1996) 1199.

[61] M.R. Emmett, F.M. White, C.L. Hendrickson, S.D.-H. Shi, A.G. Marshall, J. Am. Soc. Mass Spectrom. 9 (1998) 333.

[62] C.S. Hsu, Z. Liang, J.E. Campana, Anal. Chem. 66 (1994) 850.

[63] S. Guan, A.G. Marshall, S.E. Scheppele, Anal. Chem. 68 (1996) 46.

[64] R.P. Rodgers, K.V. Andersen, F.M. White, C.L. Hendrickson, A.G. Marshall, Anal. Chem. 70 (1998) 4743.

[65] T.M. Sack, M.L. Gross, Anal. Chem. 55 (1983) 2419.

[66] C.Q. Jiao, D.R.A. Ranatunga, W.E. Vaughn, B.S. Freiser, J. Am. Soc. Mass Spectrom. 7 (1996) 118.

[67] S.A. Hofstadler, D.A. Laude, Jr., J. Amer. Soc. Mass Spectrom., 3 (1992) 615.

[68] F.F. Chen, Introduction to Plasma Physics and Controlled Fusion, Plenum Press, New York, 1984.

[69] R.T. McIver, Jr., Int. J. Mass Spectrom. Ion Processes 98 (1990) 35.

[70] H.U. Hasse, S. Becker, G. Dietrich, N. Klisch, H.J. Kluge, M. Lindinger, K. Lutzendirchen, L. Schweikhard, J. Ziegler, Int. J. Mass Spectrom. Ion Processes 132 (1994) 181.

[71] P. Caravatti, USA. Patent No. 4,924,089, issued 8 May, 1990.

[72] S. Maruyama, L.R. Anderson, R.E. Smalley, Rev. Sci. Instrum. 61 (1990) 3686.

[73] R.T. McIver, Jr., USA Patent No. 4,523,235, issued 13 August, 1985.

[74] P.A. Limbach, A.G. Marshall, M. Wang, Int. J. Mass Spectrom. Ion Processes 125 (1993) 135.

[75] S. Guan, A.G. Marshall, J. Am. Soc. Mass Spectrom. 7 (1996) 101.

[76] M.E. Belov, M.V. Gorshkov, H.R. Udseth, G.A. Anderson, A.V. Tolmachev, D.C. Prior, R. Harkewicz, R.D. Smith, J. Am. Soc. Mass Spectrom. 11 (2000) 19.

[77] M.W. Senko, C.L. Hendrickson, M.R. Emmett, S.D.-H. Shi, A.G. Marshall, J. Am. Soc. Mass Spectrom. 8 (1997) 970.

[78] Y. Wang, S.D.-H. Shi, C.L. Hendrickson, A.G. Marshall, 47th Amer. Soc. for Mass Spectrom. Annual Conf. on Mass Spectrometry & Allied Topics, Dallas, TX, 1999, TPC 047.

[79] C.L. Hendrickson, J.P. Quinn, M.R. Emmett, amd A. G. Marshall, Proc. 47th Amer. Soc. Mass Spectrometry & Allied Topics Annual Conf. on Mass Spectrom & Allied Topics, Long Beach CA, 2000, MPB083. K.J. Auberry, M.E. Belov, E.N. Nikolaev, 47th Amer. Soc. for Mass Spectrom. Annual Conf. on Mass Spectrometry & Allied Topics, Long Beach, CA, 2000, MPB078.

[80] R.T. McIver, Jr., Y. Li, R.L. Hunter, Int. J. Mass Spectrom. Ion Processes 132 (1994) L1.

[81] J.A. Marto, S. Guan, A.G. Marshall, Rapid Commun. Mass Spectrom. 8 (1994) 615.

[82] R.L. White, C.L. Wilkins, Anal. Chem. 54 (1982) 2443.

[83] P. Kofel, M. Allemann, H. Kellerhals, K.-P. Wanczek, Int. J. Mass Spectrom. Ion Processes 72 (1986) 53.

[84] D.A.J. Laude, S.L.J. Pentoney, P.R. Griffiths, C.L. Wilkins, Anal. Chem. 59 (1987) 2283.

[85] G.W. Stockton, J.T. Meek, W.G. Millen, R.S. Wayne, in B. Asamoto (Eds.), FT-ICR/MS: Analytical Applications of Fourier Transform Ion Cyclotron Resonance Mass Spectrometry, Vol. VCH, New York, 1991, p. 235.

[86] C.C. Stacey, G.H. Kruppa, C.H. Watson, J. Wronka, F.H. Laukien, J.F. Banks, C.M. Whitehouse, Rapid Commun. Mass Spectrom. 8 (1994) 513.

[87] S.A. Hofstadler, J.H. Wahl, J.E. Bruce, R.D. Smith, J. Amer. Chem. Soc. 115 (1993) 6983.

[88] S. Guan, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 146/147 (1995) 261.

[89] F. Bloch, Phys. Rev. 94 (1954) 496.

[90] M.B. Comisarow, Adv. Mass Spectrom. 7 (1978) 1042.

[91] R.T. McIver, Jr., Rev. Sci. Instrum. 41 (1970) 555.

[92] M.B. Comisarow, Int. J. Mass Spectrom. Ion Phys. 37 (1981) 251.

[93] M.B. Comisarow, A.G. Marshall, USA Patent No. 3,937,955, issued 14 February, 1976.

[94] S.H. Lee, K.-P. Wanczek, H. Hartmann, Adv. Mass Spectrom. 8B (1980) 1645.

[95] D.P. Littlejohn, S. Ghaderi, USA Patent No. 4,581,533, issued 8 April, 1986.

[96] G. Gabrielse, L. Haarsma, S.L. Rolston, Int. J. Mass Spectrom. Ion Processes 88 (1989) 319.

[97] S.C. Beu, D.A. Laude, Jr., Int. J. Mass Spectrom. Ion Processes 112 (1992) 215.

[98] S.C. Beu, D.A. Laude, Jr., Anal. Chem. 64 (1992) 177.

[99] M. Wang, E.B. Ledford, Jr., A.G. Marshall, FACSS XIV, Detroit, MI, 1987, #43.

[100] J.A. Marto, L. Schweikhard, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 137 (1994) 9.

[101] B.S. Freiser, Int. J. Mass. Spectrom. Ion Phys. 26 (1978) 39.

[102] R. Solouki, K.J. Gillig, D.H. Russell, Anal. Chem. 66 (1994) 1583.

[103] W. Paul, H. Steinwedel, Z. Naturforsch. 8a (1953) 448.

[104] R.E. March, R.J. Hughes, Quadrupole Storage Mass Spectrometry, Wiley, New York, 1989.

[105] M.V. Gorshkov, S. Guan, A.G. Marshall, Rapid Commun. Mass Spectrom. 6 (1992) 166.

[106] S. Guan, M.V. Gorshkov, A.G. Marshall, Chem. Phys. Lett. 198 (1992) 143.

[107] D.L. Rempel, M.L. Gross, J. Amer. Soc. Mass Spectrom. 3 (1992) 590.

[108] M. Wang, A.G. Marshall, Anal. Chem. 62 (1990) 515.

[109] C.D. Hanson, M.E. Castro, E.L. Kerley, D.H. Russell, Anal. Chem. 62 (1990) 520.

[110] P.B. Grosshans, R. Chen, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 139 (1994) 169.

[111] P. Caravatti, M. Allemann, Org. Mass Spectrom. 26 (1991) 514.

[112] D.L. Rempel, R.P. Grese, M.L. Gross, Int. J. Mass Spectrom. Ion Processes 100 (1990) 381.

[113] Y. Naito, M. Inoue, Proc. 36th Amer. Soc. Mass Spectrom. Conf. on Mass Spectrom. & Allied Topics, San Francisco, CA, 1988, p. 608.

[114] Y. Wang, K.-P. Wanczek, X.Q. Jiang, Z.Y. Hua, Rev. Sci, Instrum. 64 (1993) 2585.

[115] G.S. Jackson, F.M. White, S. Guan, A.G. Marshall, J. Am. Soc. Mass Spectrom. 10 (1999) 759.

[116] S. Guan, A.G. Marshall, Rev. Sci. Instrum. 66 (1995) 63.

[117] S. Guan, X. Xiang, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 124 (1993) 53.

[118] P.B. Grosshans, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 107 (1991) 49.

[119] P.B. Grosshans, P.J. Shields, A.G. Marshall, J. Amer. Chem. Soc. 112 (1990) 1275.

[120] P. Kofel, M. Allemann, H. Kellerhals, K.P. Wanczek, in P. Longevialle (Eds.), Advances in Mass Spectrometry, Vol. 11A, Heyden & Son, London, 1989, p. 676.

[121] E.N. Nikolaev, M.V. Gorshkov, A.V. Mordehai, V.L. Talrose, Rapid Commun. Mass Spectrom. 4 (1990) 144.

[122] M. Wang, A.G. Marshall, Anal. Chem. 61 (1989) 1288.

[123] Y.P. Pan, D.P. Ridge, J. Wronka, A.L. Rockwood, Rapid Commun. Mass Spectrom. 1 (1987) 121.

[124] Y. Wang, K.-P. Wanczek, Rev. Sci. Instrum. 64 (1993) 883.

[125] Y. Huang, G.Z. Li, S. Guan, A.G. Marshall, J. Am. Soc. Mass Spectrom. 8 (1997) 962.

[126] N.I. Leont'ev, Instr. Techn. (in English) 2 (1960) 275.

[127] M.B. Comisarow, J. Chem. Phys. 69 (1978) 4097.

[128] L.S. Brown, G. Gabrielse, Rev. Mod. Phys. 58 (1986) 233.

[129] L. Schweikhard, A.G. Marshall, J. Am. Soc. Mass Spectrom. 4 (1993) 433.

[130] S. Guan, H.S. Kim, A.G. Marshall, M.C. Wahl, T.D. Wood, X. Xiang, Chem. Rev., 94 (1994) 2161.

[131] C.F. Ijames, C.L. Wilkins, Chem. Phys. Lett. 108 (1984) 58.
[132] A.G. Marshall, T.-C.L. Wang, T.L. Ricca, Chem. Phys. Lett. 108 (1984) 63.
[133] A.G. Marshall, T.-C.L. Wang, T.L. Ricca, J. Am. Chem. Soc. 107 (1985) 7893.
[134] M.B. Comisarow, A.G. Marshall, Chem. Phys. Lett. 26 (1974) 489.
[135] A.G. Marshall, T.L. Ricca, T.-C.L. Wang, USA Patent #4,761,545, issued 2 August, 1988.
[136] G. Bollen, R.B. Moore, G. Savard, H. Stolzenberg, Appl. Phys. 68 (1990) 4355.
[137] G. Savard, S. Becker, G. Bollen, H.-J. Kluge, R.B. Moore, L. Schweikhard, H. Stolzenberg, U. Wiess, Phys. Lett. A 158 (1991) 247.
[138] L. Schweikhard, S. Guan, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 120 (1992) 71.
[139] D.L. Rempel, E.B. Ledford, Jr., S.K. Huang, M.L. Gross, Anal. Chem. 59 (1987) 2527.
[140] W.J. van der Hart, W.J. van de Guchte, Int. J. Mass Spectrom. Ion Processes 82 (1988) 17.
[141] W.J. van de Guchte, W.J. van der Hart, Int. J. Mass Spectrom. Ion Processes 95 (1990) 317.
[142] D. Mitchell, S. Delong, D. Cherniak, M. Harrison, Int. J. Mass Spectrom. Ion Processes 91 (1989) 273.
[143] A.G. Marshall, P.B. Grosshans, Anal. Chem. 63 (1991) 215A.
[144] D.W. Mitchell, B.A. Hearn, S.E. DeLong, Int. J. Mass Spectrom. Ion Processes 125 (1993) 95.
[145] D.W. Mitchell, Int. J. Mass Spectrom. Ion Processes 142 (1995) 1.
[146] R. Chen, A.G. Marshall, M. Wang, Chem. Phys. Lett. 181 (1991) 168.
[147] F.R. Verdun, S.L. Mullen, T.L. Ricca, A.G. Marshall, FACSS XIV, Detroit, MI, 1987, Abstract #41.
[148] J.J. Drader, S.D.-H. Shi, G.T. Blakney, C.L. Hendrickson, D.A. Laude, A.G. Marshall, Anal. Chem. 71 (1999) 4758.
[149] P.A. Limbach, P.B. Grosshans, A.G. Marshall, Anal. Chem. 65 (1993) 135.
[150] E.R. Williams, K.D. Henry, F.W. McLafferty, J. Amer. Chem. Soc. 112 (1990) 6157.
[151] J.P. Speir, G.S. Gorman, C.C. Pitsenberger, C.A. Turner, P.P. Wang, I.J. Amster, Anal. Chem. 65 (1993) 1746.
[152] H. Sommer, H.A. Thomas, J.A. Hipple, Phys. Rev. 76 (1949) 1877.
[153] H. Sommer, H.A. Thomas, Phys. Rev. 78 (1950) 806.
[154] P.P. Genequand, Z. Angew. Math. Physik, 22 (1971) 951.
[155] R.T. Hunter, R.T. McIver, Jr., Chem. Phys. Lett. 49 (1977) 577.
[156] M. Allemann, H.-P. Kellerhals, K.-P. Wanczek, Chem. Phys. Lett. 84 (1981) 547.
[157] L. Schweikhard, M. Blundschling, R. Jertz, H.-J. Kluge, Int. J. Mass Spectrom. Ion Processes 89 (1989) R7.
[158] L. Schweikhard, M. Lindinger, H.-J. Kluge, Int. J. Mass Spectrom. Ion Processes 98 (1990) 25.
[159] N.C. Hill, G.M. Alber, L. Schweikhard, T.L. Ricca, A.G. Marshall, Proc. 39th Amer. Soc. Mass Spectrom. Conf. on Mass Spectrometry & Allied Topics, Nashville, TN, 1991, p. 1501.
[160] C.L. Hendrickson, S.A. Hofstadler, S.C. Beu, D.A. Laude, Jr., Int. J. Mass Spectrom. Ion Processes 123 (1993) 49.
[161] R. Chen, S. Guan, A.G. Marshall, J. Chem. Phys. 100 (1994) 2258.
[162] C.L. Hendrickson, J.J. Drader, D.A. Laude, Jr., J. Am. Soc. Mass Spectrom. 6 (1995) 448.
[163] G.S. Jackson, C.L. Hendrickson, B.B. Reinhold, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 165/166 (1997) 327.
[164] Y. Wang, C.L. Hendrickson, A.G. Marshall, 48th Amer. Soc. for Mass Spectrom. Annual Conf. on Mass Spectrometry & Allied Topics, Long Beach, CA, MPB080.
[165] M.B. Comisarow, V. Grassi, G. Parisod, Chem. Phys. Lett. 57 (1978) 413.
[166] F.W. McLafferty, Acc. Chem. Res., 27 (1994) 379–386.
[167] V.H. Wysocki, H.I. Kenttämaa, R.G. Cooks, Int. J. Mass Spectrom. Ion Processes 81 (1987) 181.
[168] S.A. McLuckey, D.E. Goeringer, J. Mass Spectrom., 35 (1997) 461.
[169] R.B. Cody, R.C. Burnier, B.S. Freiser, Anal. Chem. 54 (1982) 96.
[170] J.W. Gauthier, T.R. Trautman, D.B. Jacobson, Anal. Chim. Acta 246 (1991) 211.
[171] S.A. Lee, C.Q. Jiao, Y. Huang, B.S. Freiser, Rapid Commun. Mass Spectrom. 7 (1993) 819.
[172] K.A. Boering, J. Rolfe, J.I. Brauman, Int. J. Mass Spectrom. Ion Processes 117 (1992) 357.
[173] A.G. Marshall, T.-C.L. Wang, T.L. Ricca, Chem. Phys. Lett. 105 (1984) 233.
[174] C.F. Ijames, C.L. Wilkins, Anal. Chem. 62 (1990) 1295.
[175] E.R. Williams, K.D. Henry, F.W. McLafferty, J. Shabanowitz, D.F. Hunt, J. Am. Soc. Mass Spectrom. 1 (1990) 413.
[176] W.Q. Zhong, E.N. Nikolaev, J.H. Futrell, V.H. Wysocki, Anal. Chem. 69 (1997) 2496.
[177] C.J. Cassady, B.S. Freiser, D.H. Russell, Org. Mass Spectrom. 18 (1983) 378.
[178] R.L. Woodlin, D.S. Bomse, J.L. Beauchamp, J. Am. Chem. Soc. 100 (1978) 3248.
[179] D.M. Peiris, M.A. Cheeseman, R. Ramanathan, J.R. Eyler, J. Phys. Chem. 97 (1993) 7839.
[180] D.P. Little, J.P. Speir, M.W. Senko, P.B. O'Cornnor, F.W. McLafferty, Anal. Chem. 66 (1994) 2809.
[181] F.-S. Huang, R.C. Dunbar, Int. J. Mass Spectrom. Ion Processes 109 (1991) 151.
[182] D. Tholmann, D.S. Tonner, T.B. McMahon, J. Phys. Chem. 98 (1994) 2002.
[183] R.C. Dunbar, J. Phys. Chem 98 (1994) 8705.
[184] R.C. Dunbar, T.B. McMahon, D. Tholmann, D.S. Tonner, D.R. Salahub, D. Wei, J. Am. Chem. Soc. 117 (1995) 12819.
[185] W.D. Price, P.D. Schnier, R.A. Jockusch, E.F. Strittmatter, E.R. Williams, J. Am. Chem. Soc. 118 (1996) 10640.
[186] R.C. Dunbar, J. Chem. Phys. 95 (1991) 2537.
[187] M.A. Freitas, C.L. Hendrickson, A.G. Marshall, Rapid Commun. Mass Spectrom. 13 (1999) 1639.

[188] R.A. Zubarev, N.L. Kelleher, F.W. McLafferty, J. Am. Chem. Soc. 120 (1998) 3265.
[189] R.A. Zubarev, D.M. Horn, E.K. Fridriksson, N.L. Kelleher, N.A. Kruger, M.A. Lewis, B.K. Carpenter, F.W. McLafferty, Anal. Chem. 72 (2000) 563.
[190] R.B. Cody, B.S. Freiser, Anal. Chem. 59 (1987) 1054.
[191] J.D. Hogan, D.A. Laude, Jr., Anal. Chem. 62 (1990) 530.
[192] R.C. Dunbar, G.H. Weddle, J. Phys. Chem. 92 (1988) 5706.
[193] S.D.-H. Shi, C.L. Hendrickson, A.G. Marshall, Proc. Natl. Acad. Sci. USA 95 (1998) 11532.
[194] S.C. Beu, D.A. Laude, Jr., Int. J. Mass Spectrom. Ion Processes 108 (1991) 255.
[195] G.-Z. Li, S. Guan, A.G. Marshall, J. Am. Soc. Mass Spectrom. 8 (1997) 793.
[196] G.-Z. Li, H.S. Kim, S. Guan, A.G. Marshall, J. Am. Chem. Soc. 119 (1997) 2267.
[197] E.B. Ledford, Jr., D.L. Rempel, M.L. Gross, Anal. Chem. 56 (1984) 2744.
[198] M.B. Comisarow, J. Melka, Anal. Chem. 51 (1979) 2198.
[199] H.S. Kim, A.G. Marshall, J. Mass Spectrom. 30 (1995) 1237.
[200] A.T. Hsu, T.L. Ricca, A.G. Marshall, Anal. Chim. Acta 178 (1985) 27.
[201] G.M. Alber, A.G. Marshall, Appl. Spectrosc. 44 (1990) 1111.
[202] L. Chen, A.G. Marshall, Rapid Commun. Mass Spectrom. 1 (1987) 39.
[203] M. Wang, A.G. Marshall, Anal. Chem. 60 (1988) 341.
[204] M.B. Comisarow, A.G. Marshall, Can. J. Chem. 52 (1974) 1997.
[205] E.C. Craig, I. Santos, A.G. Marshall, Rapid Commun. Mass Spectrom. 1 (1987) 33.
[206] A.G. Marshall, Chem. Phys. Lett. 63 (1979) 515.
[207] A.G. Marshall, D.C. Roe, Anal. Chem. 50 (1978) 756.
[208] A.G. Marshall, Chemometrics Intelligent Lab. Syst. 3 (1988) 261.
[209] S. Guan, G.-Z. Li, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 167/168 (1998) 185.
[210] E. Bartholdi, R.R. Ernst, J. Magn. Reson. 11 (1973) 9.
[211] C.P. Williams, A.G. Marshall, Anal. Chem. 61 (1989) 428.
[212] J.J. Drader, L. Schweikhard, S.D.-H. Shi, C.L. Hendrickson, A.G. Marshall, 50th Pittsburgh Conf. on Analytical Chem. and Appl. Spectroscopy, Orlando, FL, 1999, Abstract #2065P.
[213] A. Serreqi, M.B. Comisarow, Appl. Spectrosc. 41 (1987) 288.
[214] Y. Goto, Appl. Spectrosc. 49 (1995) 1776.
[215] L. Chen, C.E. Cottrell, A.G. Marshall, Chemometrics Intelligent Lab. Syst. 1 (1986) 51.
[216] F.R. Verdun, C. Giancaspro, A.G. Marshall, Appl. Spectrosc. 42 (1988) 715.
[217] Z. Liang, A.G. Marshall, Appl. Spectrosc. 44 (1990) 766.
[218] J.F. Loo, M.D. Krahling, T.C. Farrar, Rapid Commun. Mass Spectrom. 4 (1990) 297.
[219] S. Guan, A.G. Marshall, Anal. Chem. 69 (1997) 1156.
[220] A. Rahbee, Int. J. Mass Spectrom. Ion Processes 72 (1986) 3.
[221] J.E. Meier, A.G. Marshall, Anal. Chem. 62 (1990) 201.
[222] J.E. Meier, A.G. Marshall, Anal. Chem. 63 (1991) 551.
[223] P.B. O'Connor, V. Mandelshtam, M.R. T., Proc. 47th Amer. Soc. Mass Spectrom. Conf. on Mass Spectrom. & Allied Topics, Dallas, TX, 1999, ThPB017.
[224] E.R. Williams, S.Y. Loh, F.W. McLafferty, R.B. Cody, Anal. Chem. 62 (1990) 698.
[225] P. Pfändler, G. Bodenhausen, J. Rapin, R. Houriet, T. Gäumann, Chem. Phys. Lett. 138 (1987) 195.
[226] C.W. Ross, III, S. Guan, P.B. Grosshans, T.L. Ricca, A.G. Marshall, J. Amer. Chem. Soc. 115 (1993) 7854.
[227] M.W. Senko, S.C. Beu, F.W. McLafferty, J. Am. Soc. Mass Spectrom. 6 (1995) 229.
[228] Z. Zhang, A.G. Marshall, J. Am. Soc. Mass Spectrom. 9 (1998) 225.
[229] D.M. Horn, R.A. Zubarev, F.W. McLafferty, J. Am. Soc. Mass Spectrom. 11 (2000) 320.
[230] Z. Zhang, S. Guan, A.G. Marshall, J. Am. Soc. Mass Spectrom. 8 (1997) 659.
[231] J.E. Bruce, G.A. Anderson, M.D. Brands, L. Pasa-Tolic, R.D. Smith, J. Am. Soc. Mass Spectrom. 11 (2000) 416.
[232] D.W. Mitchell, R.D. Smith, J. Mass Spectrom. 31 (1996) 771.
[233] M. Wang, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 100 (1990) 323.
[234] J.L. Beauchamp, J. Chem. Phys. 46 (1967) 1231.
[235] M.B. Comisarow, A.G. Marshall, J. Chem. Phys. 64 (1976) 110.
[236] A.G. Marshall, D.C. Roe, J. Chem. Phys. 73 (1980) 1581.
[237] P.B. Grosshans, A.G. Marshall, Anal. Chem. 63 (1991) 2057.
[238] W. Shockley, J. Appl. Phys. 9 (1938) 635.
[239] R.C. Dunbar, Int. J. Mass Spectrom. Ion Processes 56 (1984) 1.
[240] P.B. Grosshans, P.J. Shields, A.G. Marshall, J. Chem. Phys. 94 (1991) 5341.
[241] W.T. Scott, Am. J. Phys. 27 (1959) 418.
[242] P.B. Grosshans, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 100 (1990) 347.
[243] G. Jackson, J.D. Canterbury, S. Guan, A.G. Marshall, J. Amer. Soc. Mass Spectrom. 8 (1997) 283.
[244] M.B. Comisarow, in H. Hartmann, K.-P. Wanczek (Eds.), Ion Cyclotron Resonance Spectrometry Vol. II, Springer-Verlag, Berlin, 1982, p. 484.
[245] A.G. Marshall, M.B. Comisarow, G. Parisod, J. Chem. Phys. 71 (1979) 4434.
[246] A.G. Marshall, Anal. Chem. 51 (1979) 1710.
[247] R.L. White, E.B. Ledford, Jr., S. Ghaderi, C.L. Wilkins, M.L. Gross, Anal. Chem. 52 (1980) 1525.
[248] P. Langevin, Ann. Chim. Phys. 5 (1905) 245.
[249] M.B. Comisarow, J. Chem. Phys. 55 (1971) 205.
[250] S.-P. Chen, M.B. Comisarow, Rapid Commun. Mass Spectrom. 5 (1991) 450.
[251] S.-P. Chen, M.B. Comisarow, Rapid Commun. Mass Spectrom. 6 (1992) 1.
[252] D.W. Mitchell, R.D. Smith, Phys. Rev. E 52 (1995) 4366.
[253] S.D.-H. Shi, J.J. Drader, M.A. Freitas, C.L. Hendrickson, A.G. Marshall, Int. J. Mass Spectrom. 195/196 (2000) 591.
[254] T.J. Francl, M.G. Sherman, R.L. Hunter, M.J. Locke, W.D. Bowers, R.T. McIver, Int. J. Mass Spectrom. Ion Processes 54 (1983) 189.

[255] L. Schweikhard, J. Ziegler, H. Bopp, K. Lützenkirchen, Int. J. Mass Spectrom. Ion Processes 141 (1995) 77.

[256] M.V. Gorshkov, L. Pasa-Tolic, H.R. Udseth, G.A. Anderson, B.M. Huang, J.E. Bruce, P.D. C., S.A. Hofstadler, L. Tang, L.-Z. Chen, J.A. Willett, A.L. Rockwood, M.S. Sherman and R.D. Smith, J. Am. Soc. Mass Spectrom. 9 (1998) 692.

[257] S.D.-H. Shi, J.J. Drader, C.L. Hendrickson, A.G. Marshall, J. Am. Soc. Mass Spectrom. 10 (1999) 265.

[258] A.G. Marshall, S. Guan, Rapid Commun. Mass Spectrom. 10 (1996) 1819.

[259] M.W. Senko, C.L. Hendrickson, L. Pasa-Tolic, J.A. Marto, F.M. White, S. Guan, A.G. Marshall, Rapid Commun. Mass Spectrom. 10 (1996) 1824.

[260] J.W. Cooley, J.W. Tukey, Math. Comput. 19 (1965) 297.

[261] J.J. Drader, S.D.-H. Shi, M.A. Freitas, C.L. Hendrickson, A.G. Marshall, Proc. 46th Amer. Soc. Mass Spectrom. Conf. on Mass Spectrom. & Allied Topics, Orlando, FL, p. 449.

[262] S.A. Hofstadler, J.C. Severs, R.D. Smith, F.D. Swanek, A.G. Ewing, J. High Resol. Chromatogr. 19 (1996) 617.

[263] E.R. Williams, Anal. Chem. 70 (1998) 179A.

[264] R.C. Dunbar, T.B. McMahon, Science 279 (1998) 194.

[265] A.G. Marshall, M.R. Emmett, M.A. Freitas, C.L. Hendrickson, Z. Zhang, in A.L. Burlingame, S.A. Carr, M.A. Baldwin (Eds.), Mass Spectrometry in Biology and Medicine, Humana Press, Totowa, NJ, 1999, p. 31.

[266] F.W. McLafferty, E.K. Fridriksson, D.M. Horn, M.A. Lewis, R.A. Zubarev, Science 284 (1999) 1289.

[267] S.A. Lorenz, E.P.I. Maziarz, T.D. Wood, Appl. Spectrosc. 53 (1999) 18A.

[268] C.L. Hendrickson, M.R. Emmett, Annu. Rev. Phys. Chem. 50 (1999) 517.

[269] N.L. Kelleher, Chem. Biol. 7 (2000) R37.

[270] T.D. Veenstra, S. Martinovic, G.A. Anderson, L. Pasa-Tolic, R.D. Smith, J. Am. Soc. Mass Spectrom. 11 (2000) 78.

[271] A.J. Peurrung, R.T. Kouzes, Int. J. Mass Spectrom. Ion Processes 145 (1995) 139.

[272] J.T. Stults, Anal. Chem. 69 (1997) 1815.

[273] Y. Naito, M. Inoue, J. Mass Spectrom. Soc. Jpn. 42 (1994) 1.

[274] K. Qian, R.P. Rodgers, C.L. Hendrickson, M.R. Emmett, A.G. Marshall, 48th Amer. Soc. for Mass Spectrom. Annual Conf. on Mass Spectrometry & Allied Topics, Long Beach, CA, 2000, WOB3:00.

[275] R.P. Rodgers, E.N. Blumer, C.L. Hendrickson, A.G. Marshall, J. Am. Soc. Mass Spectrom. 11 (2000) 835.

[276] M.V. Gorshkov, S. Guan, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 128 (1993) 47.

[277] K.-P. Wanczek, Pittsburgh Conf. on Anal. Chem. Appl. Spectr., Atlantic City, NJ, 1987, paper No. 526.

[278] A.G. Marshall, L. Schweikhard, Int. J. Mass Spectrom. Ion Processes 118/119 (1992) 37.

[279] F. He, C.L. Hendrickson and A.G. Marshall, Anal. Chem., 73 (2001) 0000–0000.

[280] S.D.-H. Shi, C.L. Hendrickson, A.G. Marshall, W.J.J. Simonsick, D.J. Aeserud, Anal. Chem. 70 (1998) 3220.

[281] N.L. Kelleher, M.W. Senko, M.M. Siegel, F.W. McLafferty, J. Am. Soc. Mass Spectrom. 8 (1997) 380.

[282] M.A. Freitas, X. Zang,P.G. Hatcher, 48th Amer. Soc. for Mass Spectrom. Annual Conf. on Mass Spectrometry & Allied Topics, Long Beach, CA, 2000, WOC4:20.

[283] R. Chen, X. Cheng, D.W. Mitchell, S.A. Hofstadler, Q. Wu, A.L. Rockwood, M.G. Sherman, R.G. Smith, Anal. Chem. 67 (1995) 1159.

[284] L. Chen, A.G. Marshall, Int. J. Mass Spectrom. Ion Processes 79 (1987) 115.