



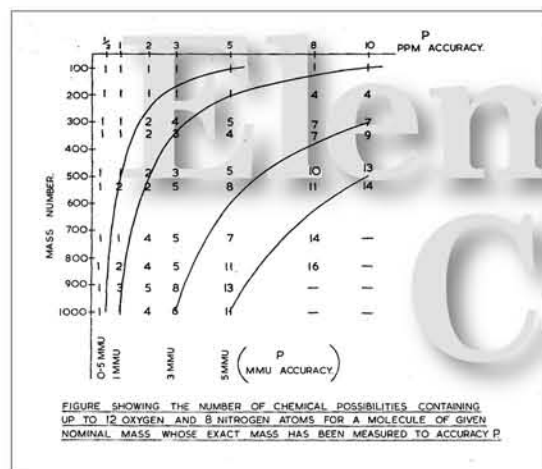
# In Search of Accurate Mass: The Unending Quest for Higher Resolving Power

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**Introduction:** In the early 50's,[1] the idea that determining the accurate mass of a compound could provide information about its elemental composition provided the impetus for developing magnetic sector instruments with increased resolving power. It was soon realized; however, that as the mass of the compound of interest increased, so to did the need for greater and greater resolving power.



## Accurate Mass Yields Elemental Composition

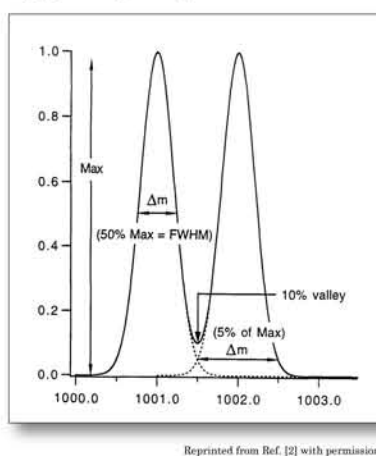
The need for more resolving power for accurate mass determination is demonstrated in the plot shown here, probably constructed sometime in the late '50s or early '60s. As the mass of the analyte and the number of heteroatoms increases, greater resolving power is required to obtain the mass measurement accuracy necessary to unambiguously determine elemental composition.

## Resolving Power or Resolution

It is common in the literature to refer to instruments capable of performing accurate mass measurements as 'high resolution' mass spectrometers. On the other hand, the definition of

resolving power is  $M$  divided by  $\Delta M$  where  $M$  is the mass at which the resolving power is determined and  $\Delta M$  is the peak width at some specific peak height on that peak. The higher the resolving power, the greater the separation between two peaks of equal nominal mass. Resolution, on the other hand, is a measure of the smallest possible distance on the mass scale separating two peaks and for a high resolving power instrument is a very small number; usually expressed in parts per million (ppm) of mass.

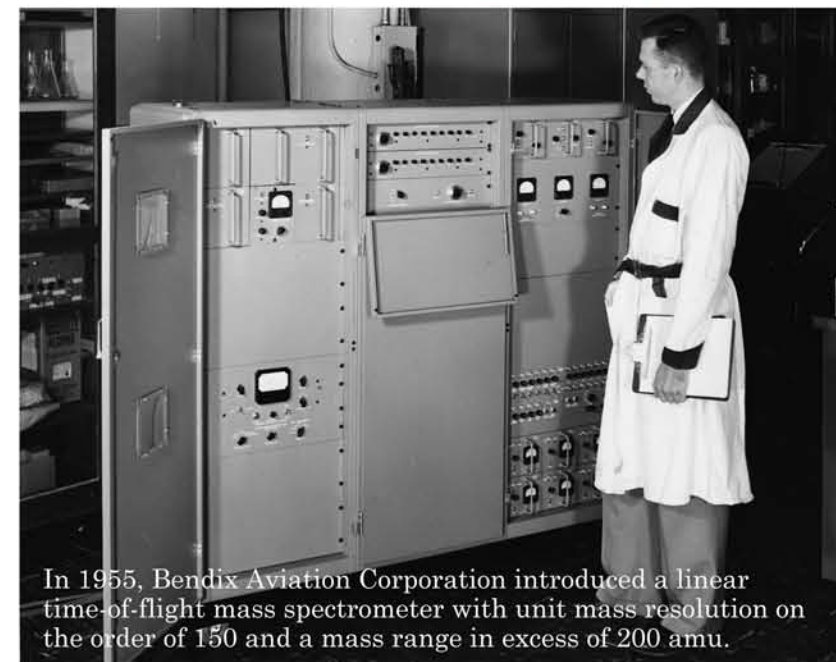
If a mass spectrometer is spoken of as a 'high resolution' instrument, that implies that the smallest possible distance on the mass scale between two peaks is large and consequently is a low resolving power instrument; contrary to the sense the speaker intends. This nomenclature problem is not helped by the fact that both IUPAC and ASMS Guidelines have in the past defined resolution and resolving power in the opposite sense above[2]. It is apparent that confusion will reign for some time on the issue of resolving power and resolution.



The details of analyzer design improvements for high resolving power sector instruments were reported in an earlier ASMS poster[3] in 2005. These improvements lead to a competition among instrument manufacturers, which came to a head in the early '80s when proponents of the Mattauch-Herzog mass spectrograph fought with proponents of the pseudo Nier-Johnson mass spectrometer for bragging rights about the best instrument for accurate mass determination measurements. Since then, other mass analyzers have come to dominate the high resolving power, accurate mass measurement arena.

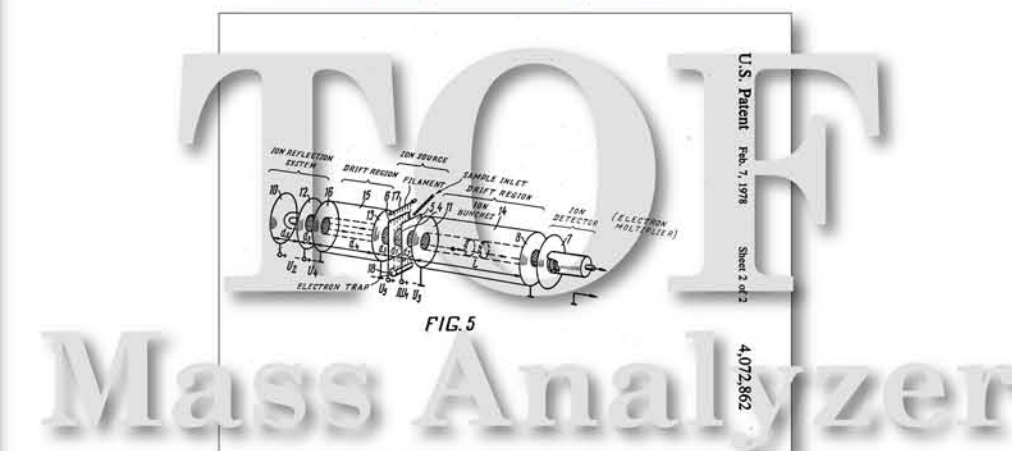
**Time-of-Flight Mass Analyzers** Although Mamyrin [4] described the principle of the reflectron time-of-flight mass spectrometer as a means of increasing the resolving power of ToF analyzers in the early '70s and filed an American patent for his design in 1976, significant commercial development didn't occur until the mid to late '90s. Mamyrin's reflectron design with the ion source located in the middle of the flight tube and the detector at one end provided resolving powers that approached those of some magnetic sector instruments.

## First Commercial Time-of-Flight mass spectrometer



In 1955, Bendix Aviation Corporation introduced a linear time-of-flight mass spectrometer with unit mass resolution on the order of 150 and a mass range in excess of 200 amu.

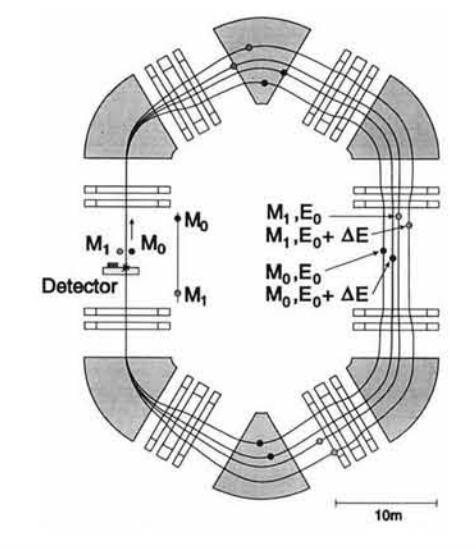
## From Mamyrin's US Patent of Reflectron Time-of-Flight Mass Spectrometer



Additional improvements in resolving power were obtained with reflectron designs in which the ion source and detector were located at the same end of the flight tube. The advantages of the latter design for improved resolving power are several:

- Increased field free region increases mass separation
- Metastable decomposition products are not seen by the detector
- Energy spread in ions can be corrected for more easily
- The detector is shielded from electromagnetic radiation and stray signals from the ion source

## Ring Time-of-Flight Mass Analyzer



With the optimization of the reflectron ToF mass analyzer by a number of instrument companies, the resolving power and mass measurement accuracy improved by orders of magnitude over the early linear ToF introduced by Bendix a half century earlier. Since ToF mass analyzer operate in pulsed mode, they are suitable for either synchronous, such as matrix assisted laser desorption ionization (MALDI), or asynchronous, such as plasma desorption (PD), ion sources. The present embodiment of ToF mass analyzers is dominated by linear reflectron instruments. However, in a review by Wollnik[5] nearly a dozen alternative mass analyzer geometries based on time-of-flight are discussed.

1932

Lawrence & Livingston describe magnet cyclotron

1946

Stephens presents paper at Cambridge American Physical Society meeting entitled "A Pulsed Mass Spectrometer with Time Dispersion"

1949

Hipple, Sommer & Thomas describe the Omegatron

1954

Alpert & Buritz describe use of Omegatron as residual gas analyzer

1956

W. C. Wiley publishes design of Bendix ToF in Science

1957

Metropolitan Vickers introduces the MS-7 Mattauch Herzog geometry instrument with spark source

1959

Consolidated Electrodynamics Corporation introduces 21-110, a high resolving power instrument with Mattauch Herzog geometry with spark source for analysis of inorganic materials

1960

Introduction of MS-9 pseudo Nier-Johnson geometry mass spectrometer

1965

Wobschall describes first non-commercial ICR based on power absorption detection

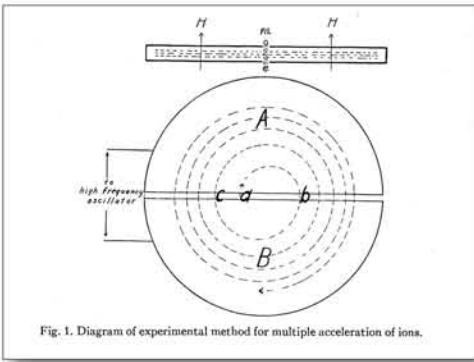
1966

Omegatron designed for use in upper atmosphere analysis by researchers at University of Michigan  
Ernst and Anderson perform first FT-NMR experiment  
ICR Double resonance technique described

1968

Llewellyn granted patent for resonant power absorption in ICR

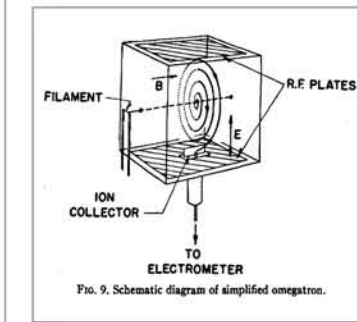




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**The Omegatron** The origins of ion cyclotron resonance mass spectrometry reach back to the work of E. O. Lawrence and S. M. Livingstone[6] at the California Institute of Technology in the early '30s. At Caltech the cyclotron was used as a tool to investigate nuclear physics. Their earliest instrument (see figure) had pole faces 280 cm in diameter and was capable of creating a nanoampere of protons at 1.2 Megavolts; using only 4000 volts accelerating potential. Lawrence was stymied in raising funds for the larger cyclotrons for which his lab became famous until after being awarded the Nobel Prize for Physics in 1939[7].

In 1949 Hipple, Sommer and Thomas[8] at the National Bureau of Standards described an instrument they called the 'omegatron'. They used it to determine fundamental physical constants, such as the Faraday[9], and the ratio of the mass of the proton to the electron[10]. Even though Hipple had obtained several patents for sector mass spectrometer designs earlier when at Westinghouse, he didn't pursue the analytical capability of the Omegatron as a mass analyzer.



Reprinted from Ref[11]

The operation of the Omegatron depends upon the creation of a beam of ions in the center of the box constituting the mass analyzer by an electron beam accelerated through the small holes in the sides of the box. The magnetic field,  $B$ , provides the cyclotron field of the Omegatron and collimation for the ionizing electron beam. Ions created in the center of the Omegatron spiral outward under the combined influence of the magnetic and electric fields. The RF plates provide a means of detecting the resonant frequency and the collector plate at the bottom of the box records the arrival of ions before they spiral into its sides.

Despite being dubbed the Omegatron, the name didn't stick and at some indeterminate time in the past, workers in this field began to refer to these instruments as ion traps.

One of the earliest applications of the Omegatron as a mass spectrometer was published by Alpert and Buritz in 1954 [11] to measure the residual gases in a vacuum system. With this instrument, they were able to determine that the slow rise in pressure in a sealed vacuum system was due to atmospheric helium leaking through the various glass parts of the vacuum system.

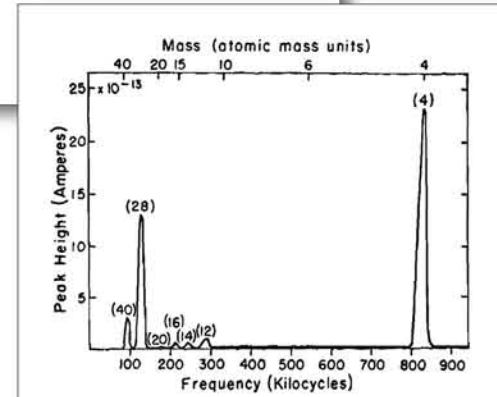


FIG. 11. Ion collector current versus impressed rf frequency. The mass scale above has been adjusted to coincide at the frequency of the mass 4 peak.

Reprinted from Ref[11]

1970	1973	1974	1976	1980	1983	1984	1985	1988	1989	1990	1994	1996	1999	2005
Trapped-ion cell developed by McIver	Mamyryn publishes reflectron design in Zh. Eksp. Teor. Fiz. "Mass reflectron. New non-magnetic time-of-flight high-resolution mass spectrometer"	Comisarow and Marshall perform first FT-ICR experiment CHIRP excitation permits observation of multiple m/z values at once	MacFarlane and Torgerson report plasma desorption ToF mass spectrometry experiment	Shooting match between AEI and CEC on ion detection (photoplate vs electrical detection)	LAMMA-1000 reflectron ToF MS described	Gross and group develop frequency/mass calibration for accurate mass determination	SWIFT excitation described by Marshall, Wang & Rica	Tanaka et al produce reflectron-ToF spectrum of 100kDa protein cluster	Dehmelt and Paul share Nobel Prize in Physics for ICR and Quadrupole ion traps respectively	Ion remeasurement techniques developed to improve S/N ratio	Hybrid magnetic sector-orthogonal axis linear ToF instrument described	Hybrid quadrupole-orthogonal axis reflectron ToF instrument described	Makarov granted patent for Orbitrap	Details of Orbitrap published.

**Fourier Transform Ion Cyclotron Resonance Mass Analyzers** The true potential of ion traps as mass analyzers was not realized until several decades later, when in 1974, Comisarow and Marshall [12] demonstrated the use of Fourier transform techniques for the ion trap. Since this seminal research, interest in FT-ICR has been intense and the last 35 years have seen a number of developments that have made instruments of this type very important in the application of mass spectrometry to biological applications.

A 'pre-FT' experiment reported in 1966[13] using a double resonance technique demonstrated the capability of ICR traps for performing tandem MS experiments. Subsequent important contributions to the development of FT-ICR traps as tandem MS instruments were made in:

- 1978 – Infrared multiphoton dissociation (IRMPD)[14],
- 1994 – Blackbody infrared radiative dissociation (BIRD)[15],
- 1998 – Electron capture dissociation (ECD) in [16].

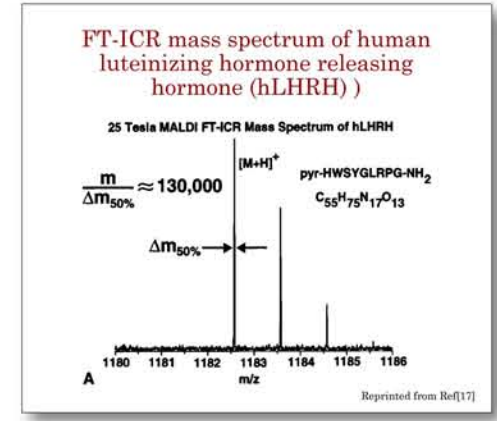
The equation describing cyclotron motion in an ion trap indicates that resolving power increases with magnetic field strength. Consequently, instrument designers are continuously implementing every new development in magnet technology to use higher field magnets for FT-ICR.

An alternative to increasing the magnetic field strength for greater resolving power is to condition the ions in the trap prior to excitation and apply more sophisticated excitation signals. A combination of techniques was developed for MALDI FT-ICR, using a gated trapping event, a radio frequency-only pressure focusing event, along with a segmented cubic trap with electrical compensation. [18] Applying all of these techniques together, researchers were able to demonstrate 850,000 resolving power for substance-P using a 3 Tesla magnet.

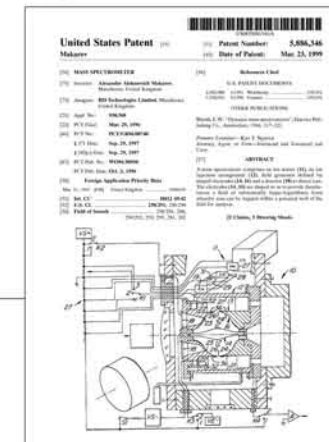
**The Orbitrap** One of the most recent developments in the field is the Orbitrap.[19] This instrument is purported to have many of the operating advantages of previous FT-ICR instruments, but without the requirement of an intense magnetic field. The use of a hyper-logarithmic electric field generated by specially shaped coaxial electrodes is essential to the performance of this mass analyzer. This instrument is capable of resolving powers up to 100,000, valley not specified.

While magnetic sector manufacturers were competing against each other in resolving power specifications in the late '80s, other mass analyzer types, notably time-of-flight and ion trap mass analyzers, were undergoing significant improvements. Coupled with the ease of interfacing sample separation technologies to these latter mass analyzers for biological applications, they underwent a surge in a development. The need for even more accurate mass determinations in protein sequencing experiments provided additional impetus to these developments. Today, the resolving power and mass measurement accuracy specifications of modern instruments surpass anything that was thought possible with magnetic sector analyzers. Thus, the high performance sector instruments of the '70s have been superseded by instruments based on time-of-flight and Fourier transform mass analyzers.

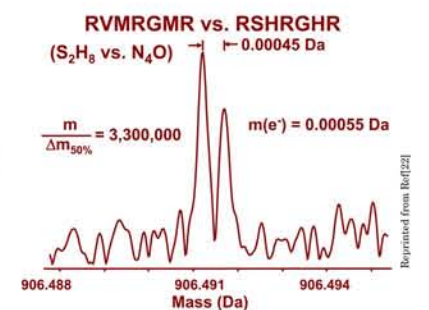
YEAR	ANALYZER	RESOLVING POWER	REFERENCE	NOTES
1942	Magnetic sector	150 Nominal Mass	C. Judson	Private Communication
1955	ToF (linear)	150 Nominal Mass	[21]	
1980	Double focusing sector	80,000 10% Valley	Commercial Literature	Various Manufacturers
1990s	Q-ToF (linear reflectron)	10,000 10% Valley	Commercial Literature	Various Manufacturers
2001	FT-ICR (9.4T magnet)	3,300,000	[22]	Full Width Half Maximum Peak Height



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Reprinted from Ref[22]



Difference in mass less than mass of the electron

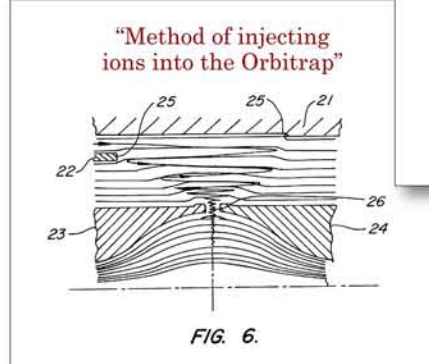


FIG. 6.

LETTERS TO THE EDITOR  
A New Method of Measuring the Period of a Simple Pendulum  
A Method of Measuring the Period of a Simple Pendulum

Reprinted from Ref[8]

LETTERS TO THE EDITOR  
The Author Will Be Grateful to the Editor for the Receipt of the Manuscript of the Paper  
A Note on the Period of a Simple Pendulum

Reprinted from Ref[11]



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