



A REVIEW ON ANALYZERS FOR MASS SPECTROMETRY

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ABSTRACT

Mass spectrometry is a technique used for measuring the molecular weight and determining the molecular formula of an organic compound. The complete process involves the conversion of the sample into gaseous ions, with or without fragmentation, which are then characterized by their mass to charge ratios (m/z) and relative abundances. The MS principle consists of ionizing chemical compounds to generate charge molecules or molecule fragments and measurement of their mass-to-charge ratio by using the one of a variety of techniques. A mass analyzer is an essential component of the mass spectrometer that after taking ionized masses separates them on the basis of charge to mass ratio and then outputs them to the detector where they are detected according to m/z ratio and converted to a digital output for an easy interpretation. The detector records either the charge induced or the current produced when an ion passes by or hits a surface and displays results in the form of spectrum. This article provides an overview of mass spectrometry, focusing on various types of analyzers used; principles of operation and current performance capabilities of mass analyzers and their significance in the development of mass spectrometry in molecular analysis, while briefly touching on ion detectors and the concept of vacuum in a mass spectrometer.

KEYWORDS: *Quadrupole, Quadrupole ion trap, Fourier Transform Ion Cyclotron Resonance, Time of Flight, Magnetic sector, Detectors.*



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Received on: 02-08-2017

Revised and Accepted on: 20-09-2017

DOI: <http://dx.doi.org/10.22376/ijpbs.2017.8.4.p139-151>



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INTRODUCTION

Mass Spectrometry is a powerful technique for identifying unknowns, studying molecular structure, and probing the fundamental principles of chemistry. Mass spectrometry is essentially a technique for "weighing" molecules. Mass spectrometry is based upon the motion of a charged particle, called an ion, in an electric or magnetic field. The mass to charge ratio (m/z) of the ion affects this motion. Since the charge of an electron is known, the mass to charge ratio a measurement of an ion's mass. Typical mass spectrometry research focuses on the formation of gas phase ions, the chemistry of ions, and applications of mass spectrometry.¹ The main objective of this article is to give a brief review of mass spectrometer and useful information about the various mass analyzers including their principle of operation, benefits, limitations and applications in mass spectrometry. Along with this it is also aimed to provide a brief introduction of various detectors used and also the importance of vacuum in mass spectrometry.

DEFINITIONS

MASS SPECTROMETRY

It is a technique used to measure the characteristic of a sample or molecule i.e., chemical composition and structure. This will be happened by converting the material to charged molecules to measure their mass to charge ratio.²

MASS SPECTROMETER

It is an instrument in which the substances in gaseous or vapor state is bombarded with a beam of electrons, to form positively charged ions (cations) which are further sorted according to their mass to charge ratio to record their masses and relative abundances.

MASS SPECTRUM

It is a sorted collection of the masses of all the charged molecular fragments produced, the relative abundance of each is the characteristics of every compound. The mass spectrum can give detail information about composition of an organic compound and the position of functional groups and is also used for the determination of molecular weight.³

AREAS IN WHICH MASS SPECTROMETRY IS USED

This technique is used in industrial and academic fields for both routine and research purposes. The following list will clarify the major mass spectrometric applications

PHARMACEUTICAL

To determine chemical structure of drugs and drug metabolites; determination of molecular weights; differentiation between cis and trans isomeric forms; screening for metabolites in biological systems; synthesis of drug candidates and their screening; identification of impurities and their profiling; stability studies of drug substances and drug formulations.

CLINICAL

To perform forensic analysis such as confirmation of drug abuse; to detect disease biomarkers e.g., newborns screened for metabolic diseases; for hemoglobin analysis.

ENVIRONMENTAL

To test water quality and food contamination.

GEOLOGICAL

To measure petroleum composition and perform carbon dating.

BIOTECHNOLOGY

Determination of structure, function, folding and interactions of proteins; monitoring of enzyme reactions, chemical modifications and protein digestion; detection of specific post-translational modifications throughout complex biological mixtures.²⁻³

MASS ANALYZERS

With the advent of ionization sources that can vaporize and ionize molecules, it has become necessary to improve mass analyzer performance with respect to speed, accuracy, and resolution. The first mass analyzers, made in the early 1900's, used magnetic fields to separate ions according to their radius of curvature through the magnetic field. The design of modern analyzers has changed significantly in the last few years, now offering much higher accuracy, increased sensitivity, broader mass range, and the ability to give structural information. Because ionization techniques have evolved, mass analyzers have been forced to change in order to meet the demands of analyzing a wide range of bio-molecular ions with part per million mass accuracy and sub femtomole sensitivity.⁴

GENERAL PRINCIPLE OF OPERATION OF MASS ANALYZER

Once analyte ions are formed in the gas phase, a variety of *mass analyzers* are available and used to separate the ions according to their *mass-to-charge ratio* (m/z). Mass spectrometers operate with the dynamics of charged particles in electric and magnetic fields in vacuum described by the Lorentz force law and Newton's second law of motion

$$F = z(E + v \times B) \text{ (Lorentz force equation)}$$

$$F = ma \text{ (Newton's second law of motion)}$$

Where 'F' is the force applied to the ion, m is the mass of the ion, 'a' is the acceleration, 'q' is the ionic charge, 'E' is the electric field, and 'v x B' is the vector cross product of the ion velocity and the magnetic field. Combining those equations results in the equation that describes the motion of charged particles

$$(m/z)a = E + v \times B$$

Two particles with the same physical quantity m/z behave identically, and all mass spectrometers measure m/z rather than m .⁵

PERFORMANCE CHARACTERISTICS OF MASS ANALYZERS

This is the ability of the analyzer to separate different molecular ions, generate fragment ions from a selected ion, and then mass measure the fragmented ions. The fragmented ions are used for structural determination of original molecular ions. The characteristics of these mass analyzers are

1. Resolution describes the ability of a mass analyzer to separate adjacent ions.
2. Mass accuracy is the ability of a mass analyzer to assign the mass of an ion close to its true mass.
3. Mass range is usually defined by the lower and upper m/z value observed by a mass analyzer.
4. Sensitivity is the ability of a particular instrument to respond to a given amount of analyte.
5. Scan speed is the rate at which we can acquire a mass spectrum, generally given in mass units per unit time.
6. Tandem mass spectrometry (MS/MS; or MS_n , $n=1,2,3\dots$) provides the ability to mass-analyze sample components sequentially in time or space to improve selectivity of the analyzer or promote fragmentation and facilitate structural elucidation.⁴

TYPES OF ANALYZERS

Analyzers are typically described as either continuous or pulsed.

CONTINUOUS ANALYZERS

These analyzers are similar to a filter or monochromator used for optical spectroscopy. They transmit a single selected m/z to the detector and the mass spectrum is obtained by scanning the analyzer so that different mass to charge ratio ions are detected. They include:

- Quadrupole filters and
- Magnetic sectors.

PULSED MASS ANALYZERS

These are the other major class of mass analyzer. These are less common but they have some distinct advantages. These instruments collect an entire mass spectrum from a single pulse of ions. This results in a signal to noise advantage similar to Fourier transform or multichannel spectroscopic techniques. Pulsed analyzers include:

- Time-of-flight,
- Ion cyclotron resonance,
- Quadrupole ion trap mass spectrometers.¹

There are six general types of mass analyzers that can be used for the separation of ions in a mass spectrometry.

1. Quadrupole Mass Analyzer
2. Magnetic Sector and Electrostatic Sector Mass Analyzer
3. Time of Flight Mass Analyzer
4. Quadrupole Ion Trap Mass Analyzers
5. Fourier Transform Ion Cyclotron Resonance Mass Analyzer⁶

QUADRUPOLE MASS ANALYZER

Quadrupole mass analyzer is one type of mass analyzer used in mass spectrometry. A typical quadrupole mass analyzer consists of four rods with a hyperbolic cross section that are accurately positioned parallel in a radial array. The quadrupole rods are typically constructed using molybdenum alloys because of their inherent inertness and lack of activity. Very high degrees of accuracy and precision (in the micrometer region) in rod machining and relative positioning are required to achieve unit mass accuracy.⁷ Quadrupole mass spectrometers ~QMSs' are widely used in both industry and research for fast accurate analysis of gas and vapors. An example of how a QMS may be used is in a semiconductor fabrication plant as a residual gas analyzer. The QMS contains basically three elements; i) ion source, ii) mass filter, and iii) ion detector.⁸ (Figure 1)

PRINCIPLE OF OPERATION

Quadrupole mass analyzer consists of a pair of positive and negative rods arranged in an alternate manner because of the "RF voltage" which continues to oscillate at a radio frequency. An ion passing through the quadrupole analyzer will successively be attracted and then repelled from each rod until it reaches the "saddle" field. At a given DC/RF combination, only the ions of a particular m/z show a stable trajectory and are transmitted to the detector, while ions with unstable trajectories do not pass the mass filter, because the amplitude of their oscillation becomes infinite. Thus, the quadrupole acts as a variable band pass filter. By changing DC and RF in time, usually at a fixed ratio, ions with different m/z values can be transmitted to the detector one after another. The relationship between the DC and alternating current (RF) voltages and the mass-to-charge ratio of stable ions can be plotted on a Mathieu diagram. Quadrupole rods may be "tuned" using a compound that reproducibly fragments to give ions of particular mass-to-charge ratio such as perfluoro-tributylamine is used for tuning the quadrupole in electron ionization gas chromatography–mass spectrometry (GC–MS). Furthermore, the DC and RF voltages can be adjusted to alter the resolution and sensitivity of the device. This operation is typically carried out using an automated instrument algorithm.⁷⁻⁸

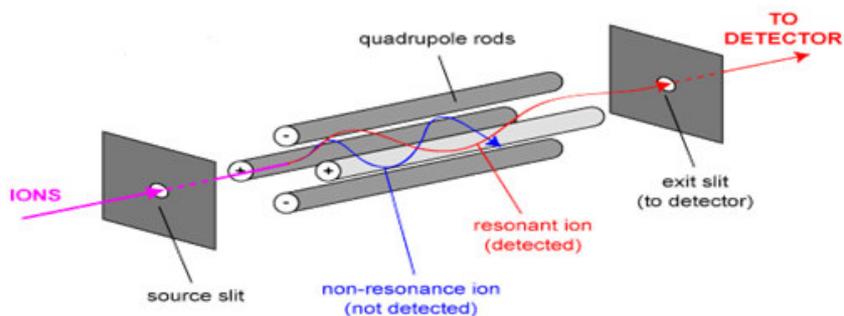


Figure 1A
Schematic Diagram of a Quadrupole Analyzer⁹

The quadrupole mass filter can be operated in four modes.

- (i) It can be applied in full-spectrum mode by scanning DC and RF in a fixed ratio, providing generally unit-mass resolution and nominal mono-isotopic mass determination with great ease of operation, versatility, fast scanning, and limited costs. Scan speeds as high as $10\,000\text{ u s}^{-1}$ can be achieved.
- (ii) Alternatively, it can be applied in selected-ion monitoring (SIM) mode, dwelling on selected m/z values, and capable of rapidly switching (within $\leq 5\text{ ms}$) between different m/z values. In SIM mode, significantly improved S/N can be achieved, making the SIM mode of a quadrupole ideal for routine targeted quantitative analysis.
- (iii) In RF-only mode, the quadrupole can be used as an ion-transport and focusing device. As such, RF-only quadrupole and related hexapole or octapole devices have been used in vacuum interfaces of API-MS systems and as collision cells and/or ion-transport devices in MS–MS instruments.
- (iv) Finally, a quadrupole mass analyzer can be applied as a linear ion trap (LIT), providing similar features as the conventional three-dimensional ion traps.

The majority of mass spectrometers installed and used are based on quadrupole mass analyzer technology.¹⁰

BENEFITS

- Classical mass spectra.
- Good repeatability.
- Relatively small and cost-effective systems.
- Low-energy collision-induced dissociation (CID) MS/MS spectra in triple quadrupole and hybrid mass spectrometers lead to efficient conversion of precursor to product.

LIMITATIONS

- Limited resolution
- Peak heights are variable as a function of mass discrimination.
- Peak height vs. mass response should be 'tuned'.
- Not compatible for pulsed ionization methods.
- Low-energy collision-induced dissociation (CID) MS/MS spectra in triple quadrupole and hybrid mass spectrometers rely most probably on energy, collision gas, pressure, and alternative factors.

APPLICATIONS

- Majority of bench top GC/MS and LC/MS systems.
- Triple quadrupole MS/MS systems.
- Sector / quadrupole hybrid MS/MS systems.¹¹⁻¹²

MAGNETIC SECTOR MASS ANALYZER

Sector mass analyzers are the most mature of the MS mass analysis technologies, having enjoyed widespread use from the 1950s through to the 1980s. The first mass spectrometer, built by J.J. Thompson in 1897, used a magnet to measure the m/z value of an electron. Magnetic sector instruments have evolved from this same concept. Magnetic sectors bend the trajectories of ions accelerated from an ion source into circular paths; for a fixed accelerating potential, typically set between 2 and 10 kV, the radii of these paths are determined by the momentum-to-charge ratios of the ions. In such a manner, the ions of differing m/z are dispersed in space. Magnetic sector instruments are often used in series with an electric sector, high resolution and tandem mass spectrometry experiments. When utilizing a magnetic sector alone, resolutions of only a few hundred can be obtained. This is primarily due to limitations associated with differences in ion velocities. To correct for this, electric sectors can be placed before or after the magnetic sector and is thus called as double focusing sector instruments.¹³

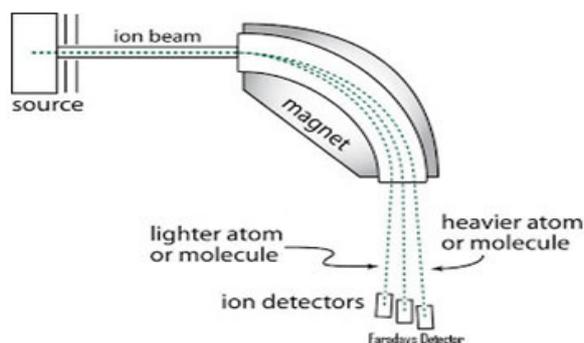


Figure 2A
Schematic Diagram of Magnetic Sector Analyzer¹⁴

PRINCIPLE OF OPERATION

Magnetic sector analyzers are similar to time of flight (TOF) analyzer in which the ions are accelerated through a flight tube, where these are separated according to charge to mass ratios. The distinction between magnetic sector and TOF is that, in the former a magnetic field is employed to separate the ions. As moving charges enter a magnetic field, the charge is deflected to a circular motion of a unique radius in a direction perpendicular to the applied magnetic field (Figure II). Ions within the magnetic field experience two equal forces namely force as a result of magnetic field and centripetal force.

$$F_B = zvB = F_c = \frac{mv^2}{r}$$

The above equation can then be rearranged to give

$$v = \frac{Bzr}{m}$$

If this equation is substituted into the kinetic energy equation

$$KE = zV = \frac{mv^2}{2}$$

$$\frac{m}{z} = \frac{B^2 r^2}{2V}$$

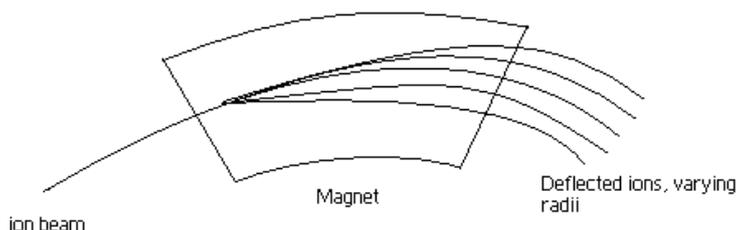


Figure 3A
Magnetic Sector Separator⁶

Basically the ions of a certain m/z value will have a unique path radius which can be determined if both magnetic field magnitude B , and voltage difference V for region of acceleration are held constant. When similar ions pass through

the magnetic field, they all will be deflected to the same degree and will all follow the same trajectory path (Figure III). Those ions which are not selected by V and B values will collide with either side of the flight tube wall or will not pass through the slit to the detector. Magnetic sector analyzers are used for mass focusing, they focus angular dispersions.^{6,15} The radius of this arc (r) depends upon the momentum of the ion (μ), the charge of the ion (C) and the magnetic field strength (B).

$$r = \frac{\mu}{C \times B}$$

Ions with greater momentum will follow an arc with a larger radius. This separates ions according to their momentum, so magnetic sectors are often called momentum analyzers.¹

ELECTRIC SECTOR/DOUBLE FOCUSING MASS SPECTROMETERS

An electric sector consists of two concentric curved plates. A voltage is applied across these plates to bend the ion beam as it travels through the analyzer. The voltage is set so that the beam follows the curve of the analyzer. The radius of the ion trajectory (r) depends upon the kinetic energy of the ion (V) and the potential field (E) applied across the plates.

$$r = \frac{2V}{E}$$

The electric sector is not useful as a standalone mass analyzer. An electric sector is, however, useful in series with a magnetic sector. The mass resolution of a magnetic sector is limited by the kinetic energy distribution (V) of the ion beam. An electric sector significantly improves the resolution of the magnetic sector by reducing the kinetic energy distribution of the ions.¹

DOUBLE FOCUSING SEPARATION

Because the magnetic sector separates on basis of momentum ions with little difference in translational energy are not focused in the same point. The spread in translational energy of the ions formed in an electron impact source limits the resolving power. In addition, source contamination leading to charging effects and contact potentials worsens this. Other ion sources like field desorption produce ions with an even larger spread in translational energy. In a double focusing mass spectrometer, the ions are lead through a radial electrostatic field prior to magnetic separation. Therefore, only ions with the same kinetic energy are fed to the magnetic sector. In this way, the electrostatic analyzer acts as a 'source' and the combination of the two sectors can be designed to have velocity-focusing properties. After acceleration, the ions possess a kinetic energy given by

$$E_{kin} = zeU = \frac{1}{2}mv^2$$

A narrow slit placed in the image plane of an electrostatic sector can be used as ion source for a magnetic sector instrument. The energy filtering gives better resolution but gives loss of sensitivity due to the rejection of ions. By a proper choice in the combination of magnetic and electrostatic sectors, the velocity dispersion is equal and opposite in both sectors.¹⁶

BENEFITS

- Classical mass spectra.
- Very high reproducibility.
- High resolution.
- High sensitivity.
- High dynamic range.

LIMITATIONS

- Not well-suited for pulsed ionization methods (e.g. MALDI).
- Usually larger and higher cost than other mass analyzers.

APPLICATIONS

- All organic MS analysis methods.
- Accurate mass measurement.
- Isotope ratio measurements.
- Quantitation.¹¹⁻¹²

TIME OF FLIGHT ANALYZER

A time-of-flight (TOF) mass spectrometer is a non-scanning mass analyzer that emits pulses of ions (or transients) from the source. These ions are accelerated so that they have equal kinetic energy before entering a field free drift region, also known as the flight tube.¹⁷ A time-of-flight (TOF) instrument consists of a pulsed ion source, an accelerating grid, a field-free flight tube, and a detector.¹⁰ (Figure IV)

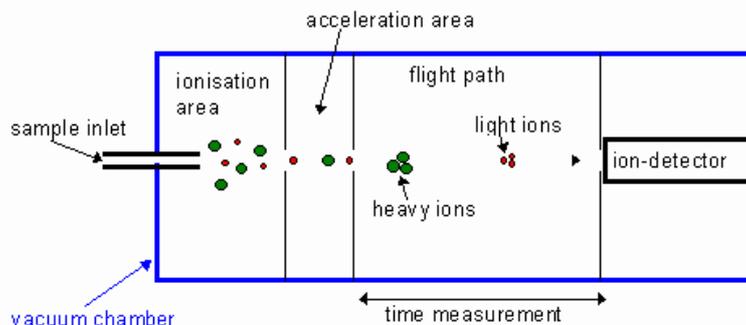


Figure 4A
Schematic of Time of Flight Analyzer¹⁸

DIFFERENT MODES OF TIME OF FLIGHT ANALYZERS

The mass analyzer used in TOF-MS can be either be a linear flight tube, applying a bended geometry the flight path to reduce the influence of neutral particles (Poschenrieder type) or a employ one (V-type) or more reflectrons (W-type) to enhance the path length within a given flight tube.

- Linear TOF (high mass range but low mass resolution)
- Reflectron TOF (lower mass range but high mass resolution)

LINEAR TOF

- Transmittance as high as 90%.
- Ions introduced into the flight tube have a temporal and kinetic energy distribution which yields relatively poor mass resolution.
- Kinetic energy spread can be reduced by employing Delayed Ion Extraction.

PRINCIPLE OF DELAYED ION EXTRACTION

- Ions are formed during a short pulse of a few nanoseconds.
- The acceleration (extraction) field is only applied after a delay of some hundreds of nanoseconds.
- At the beginning of the extraction ions with high initial velocities have traveled further than slower ones. Therefore after the second extraction pulse they do not experience the full acceleration potential.
- Thus the initially faster ions will be accelerated less than the initially slower ions.

REFLECTRON TOF

Same m/z but different kinetic energy

- In a reflectron TOF, the ions traverse the drift tube and penetrate into an electric field (ion mirror) where their direction is reversed.
- Faster ions (with higher kinetic energy) penetrate farther into the electric field than slower ions (with lower kinetic energy).
- Thus faster ions have a longer flight path and therefore need approximately the same flight time as the slower ions which have a shorter flight path.¹⁹

PRINCIPLE OF OPERATION

Time-of-flight mass spectrometry (TOFMS) is a method of mass spectrometry in which an ion's mass-to-charge ratio is determined via a time measurement. Ions are accelerated by an electric field of known strength. This acceleration results in an ion having the same kinetic energy as any other ion that has the same charge.

$$KE = zeV = \frac{mv^2}{2}$$

The velocity of the ion depends on the mass-to-charge ratio (heavier ions of the same charge reach lower speeds, although ions with higher charge will also increase in velocity).

$$v = \sqrt{\frac{2zeV}{m}}$$

The time that it subsequently takes for the ion to reach a detector at a known distance is measured. This time will depend on the velocity of the ion, and therefore is a measure of its mass-to-charge ratio. From this ratio and known experimental parameters, one can identify the ion. The flight time t needed by the ions with a particular m/z , accelerated by a potential V , to reach the detector placed at a distance d , can be calculated from

$$t = d \times \sqrt{\frac{m}{2zeV}}$$

Pulsing of the ion source is required to avoid the simultaneous arrival of ions of different m/z at detector.¹⁹⁻²⁰

BENEFITS

- Fastest MS analyzer.
- Well suited for pulsed ionization methods (method of choice for majority of MALDI mass spectrometer systems).
- High ion transmission.
- MS/MS information from post-source decay.
- Highest practical mass range of all MS analyzers.

LIMITATIONS

- Requires pulsed ionization method or ion beam switching (duty cycle is a factor).
- Fast digitizers used in TOF can have limited dynamic range.
- Limited precursor-ion selectivity for most MS/MS experiments.

APPLICATIONS

- Almost all MALDI systems.
- Very fast GC/MS systems,^{11,20}

QUADRUPOLE ION TRAP ANALYZER

The Quadrupole ion storage trap mass spectrometer (QUISTOR) is a recently developed mass analyzer with some special capabilities. Several commercial instruments are available and this analyzer is becoming more popular. QUISTORs are very sensitive, relatively inexpensive, and scan fast enough for GC/MS experiments.¹ The quadrupole ion trap is an extraordinary device that functions both as an ion store in which gaseous ions can be confined for a period of time, and as a mass spectrometer of large mass range variable mass resolution, and high sensitivity. As a storage device, the quadrupole ion trap confines gaseous ions, which are either positively or negatively charged and when required ions of each polarity also. The confining capacity of the quadrupole ion trap arises from the formation of a trapping potential well when appropriate potentials are applied to the electrodes of the ion trap.²¹ A typical (three-dimensional quadrupole) ion trap consists of a cylindrical ring electrode and two end-cap electrodes. The end-cap electrodes contain holes for the introduction of ions from an external ion source and for the ejection of ions toward an external detector. A He bath gas (~1 mbar) is used to stabilize the ion trajectories in the trap (Figure V). The basic mass analysis process consists of two steps, performed consecutively in time:

- Injection of ions by means of an ion injection pulse of variable duration and storage of the ions in the trap by application of an appropriate low RF voltage to the ring electrode and
- Ramping the RF voltage at the ring electrode to consecutively eject ions with different m/z values from the trap toward the external detector (resonant ion ejection).^{10, 21}

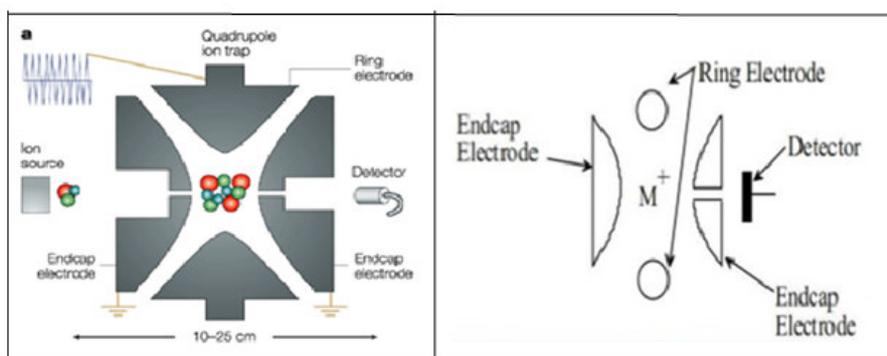


Figure 5A
Schematic Diagram of Quadrupole Ion Trap Analyzer²²

PRINCIPLE OF OPERATION

The quadrupole ion trap typically consists of a ring electrode and two hyperbolic endcap electrodes. The motion of the ions induced by the electric field on these electrodes allows ions to be trapped or ejected from the ion trap. In the normal mode, the radio frequency is scanned to resonantly excite and therefore eject ions through small holes in the endcap to a detector. As the RF is scanned to higher frequencies, higher m/z ions are excited, ejected, and detected. A very useful feature of ion traps is that it is possible to isolate one ion species by ejecting all others from the trap. The isolated ions can subsequently be fragmented by collisional activation and the fragments detected.^{4,23}

BENEFITS

- High sensitivity,
- Compactness and mechanical simplicity
- Ion/molecule reactions can be studied for mass-selected ions,
- High resolution

- Non-destructive detection is available using Fourier transform techniques.
- Multi-stage mass spectrometry (analogous to FTICR experiments)²⁴

LIMITATIONS

- Poor quantitation.
- Very poor dynamic range which can be compensated for by employing auto-ranging).
- Collision energy not well-defined in Collision Induced Dissociation [CID] MS/MS.
- Quality of the mass spectrum is influenced by many parameters such as excitation, trapping, and detection conditions.
- Mass measurement accuracy is relatively poor.

APPLICATIONS

- Benchtop GC/MS, LC/MS and MS/MS systems.
- Target compound screening.
- Ion chemistry.
- Non-destructive ion detection.^{11,24}

FOURIER-TRANSFORM ION CYCLOTRON RESONANCE MASS ANALYZER

Fourier transform ion cyclotron resonance mass spectrometry is a type of mass analyzer (or mass spectrometer) for determining the mass-to-charge ratio (m/z) of ions based on the cyclotron frequency of the ions in a fixed magnetic field. FT-ICR is the highest performance mass spectrometry technique available, offering unrivalled resolution and mass accuracy.²⁵ A Fourier-transform ion cyclotron resonance mass spectrometer (FT-ICR-MS) can be considered an ion-trap system, where the ions are trapped in a magnetic rather than in a quadrupole electric field. The Ion Cyclotron Resonance (ICR) mass spectrometer uses a superconducting magnet to trap ions in a small sample cell. This type of mass analyzer has extremely high mass resolution and is also useful for tandem mass spectrometry experiments.¹⁰ The Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FTICRMS or FTMS) consists of an ion source (in this case an Electrospray ion source), some ion optics to transfer the ions into the magnetic field (in this case an RF-Only Quadrupole ion guide), and the Ion Cyclotron Resonance (ICR) cell or Penning trap.²⁶

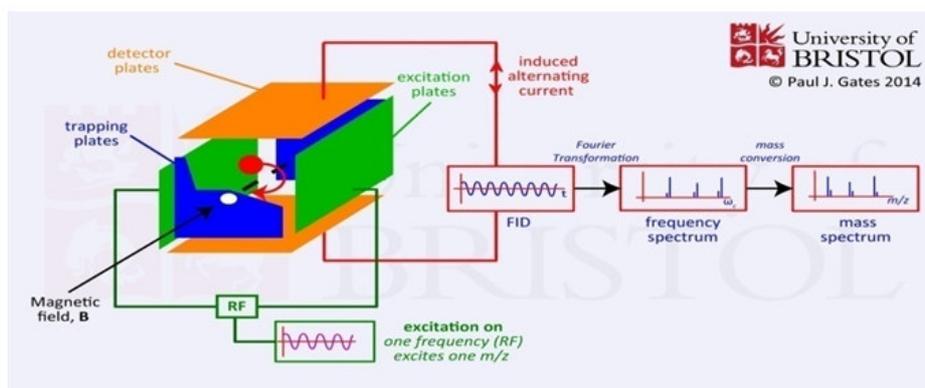


Figure 6A
Schematic Diagram of an FTICR Analyzer²⁷

PRINCIPLE OF OPERATION

Fourier transform ion cyclotron resonance mass spectrometry is a type of mass analyzer that is based on the cyclotron frequency of the ions in a fixed magnetic field to determine the m/z ratio of the ions. The ions are trapped in a Penning trap which comprises of a magnetic field with electric trapping plates, where they are excited at their resonant cyclotron frequencies to a larger cyclotron radius by an oscillating electric field orthogonal to the magnetic field. After the removal of excitation field, the ions continue to rotate at their cyclotron frequency as a "packet" of ions which induces a charge on a pair of electrodes, as the packets of ions pass close to them (Figure VI). The resulting signal is called as free induction decay (FID), that consist of a superposition of sine waves, which is then subjected to a Fourier transform to give a mass spectrum.

$$F = zv \times B$$

$$\omega_c = \frac{zB}{2\pi m}$$

$$m/z = \frac{B}{2\pi\omega_c}$$

Where,

- F is the Lorentz Force observed by the ion upon entering the magnetic field
- B is the magnetic field strength (constant)
- v is the incident velocity of the ion
- ω_c is the induced cyclotron frequency
- m is the mass of the ion
- z is the charge on the ion

FTICR-MS differs significantly from other mass spectrometry techniques in that the ions are not detected by hitting a detector such as an electron multiplier but only by passing near detection plates. Additionally the masses are not resolved in space or time as with other techniques but only by the ion cyclotron resonance (rotational) frequency that each ion produces as it rotates in a magnetic field. This provides an increase in the observed signal to noise ratio owing to the principles of Fellgett's advantage. In FTICR-MS, resolution can be improved either by increasing the strength of the magnet (in tesla) or by increasing the detection duration.²⁵⁻²⁸

BENEFITS

- Highest mass resolution of all mass spectrometers.
- Well-suited for ion chemistry and MS/MS experiments.
- Well-suited to be used with pulsed ionization techniques like MALDI,
- Non-destructive ion detection; ion re-measurement.
- Mass calibration is stable in FTICR systems with superconducting magnet.

LIMITATIONS

- Dynamic range is limited.
- Strict low-pressure requirements demand a mandatory external source for a number of analytical applications.
- Subject to space charge effects and ion molecule reactions.
- Artifacts like harmonics and sidebands are present in the mass spectra.
- Quality of the mass spectrum is influenced by many parameters such as excitation, trapping, and detection conditions).
- Generally low-energy Collision Induced Dissociation, therefore the spectrum depends on collision energy, collision gas, and other parameters.

APPLICATIONS

- Ion chemistry.
- High-resolution MALDI and electrospray experiments for high-mass analytes.
- Laser desorption for materials and surface characterization.¹¹

Table I represent the general comparison of various characteristics of all the above described mass analyzers and is as follows.

Table 1
General Comparison of Various Mass Analyzers²⁹

Characteristics	Magnetic sector	Quadrupole	Quadrupole ion trap (qit)	Time of flight (tof)	Fourier transform ion cyclotron resonance (fticr)
Quantity Measured	Momentum/charge	Filters for m/z	Frequency	Flight time	Frequency
Mass Analysis Equation	14-24	14-29	14-32	14-27	14-35
Mass to Charge Range	10^4	10^3 - 10^4	10^4 - 10^5	10^6	10^5
Resolution	10^5	10^3	10^3 - 10^4	10^3 - 10^4	10^6
Mass Measurement Accuracy	<5 ppm	0.1%	0.1%	0.1-0.01%	<10 ppm
Dynamic Range	10^7	10^5	10^4	10^4	10^4
Operating Pressure (torr)	10^{-6}	10^{-5}	10^{-3}	10^{-6}	10^{-9}
Typical Mass Range and Resolution	Range m/z 20,000 Resolution 10,000	Range m/z 3000 Resolution 2000	Range m/z 2000 Resolution 1500	Range m/z ∞ Resolution 350	Range m/z 10,000 Resolution 30,000
Advantages	•Capable of high resolution •Capable of exact	•Tolerant of high pressures •Small size	•Medium resolution •Small size •Relatively low cost	•Highest mass range •Very fast scan	•High resolution •Well suited for tandem MS

	<ul style="list-style-type: none"> mass •Medium mass range •Can be very reliable, manufacturer dependent 	<ul style="list-style-type: none"> •Well suited for electrospray •Ease of switching between positive and negative ions •Relatively low cost 	<ul style="list-style-type: none"> and simple design •Well designed for Tandem MS •Easy for positive/negative ions 	<ul style="list-style-type: none"> speed •Good adaptability to MALDI •Simple design, low cost 	
Disadvantages	<ul style="list-style-type: none"> •Not well suited for LC (CE)-MS •Not tolerant of high pressures •Instrumentation is massive •Expensive 	<ul style="list-style-type: none"> •Low resolution •Low scanning speed •Poor adaptability to MALDI 	<ul style="list-style-type: none"> •Limited mass range, however, progress is being made •Low scanning speed 	<ul style="list-style-type: none"> •Difficult LC (CE)-MS coupling •Low resolution •Difficulty of adaptation to electrospray 	<ul style="list-style-type: none"> •High vacuum ($<10^{-5}$ Torr) required •Superconducting magnet required •Expensive instrumentation •Massive

DETECTORS

Once the ions are separated by the mass analyzer, they reach the ion detector, which generates a current signal from the incident ions. The most commonly used detector is the electron multiplier, which transfers the kinetic energy of incident ions to a surface that in turn generates secondary electrons. However, a variety of approaches are used to detect ions depending on the type of mass spectrometer.⁴

ELECTRON MULTIPLIER

Perhaps the most common means of detecting ions involves an electron multiplier, which is made up of a series (12 to 24) of aluminum oxide (Al_2O_3) dynodes maintained at ever increasing potentials. Ions strike the first dynode surface causing an emission of electrons. These electrons are then attracted to the next dynode held at a higher potential and therefore more secondary electrons are generated. Ultimately, as numerous dynodes are involved, a cascade of electrons is formed that results in an overall current gain on the order of one million or higher. The high energy dynode (HED) uses an accelerating electrostatic field to increase the velocity of the ions. Since the signal on an electron multiplier is highly dependent on ion velocity, the HED serves to increase signal intensity and therefore sensitivity.

FARADAY CUP

A Faraday cup involves an ion striking the dynode (BeO, GaP, or CsSb) surface which causes secondary electrons to be ejected. This temporary electron emission induces a positive charge on the detector and therefore a current of electrons flowing toward the detector. This detector is not particularly sensitive, offering limited amplification of signal, yet it is tolerant of relatively high pressure.

PHOTOMULTIPLIER CONVERSION DYNODE

The photomultiplier conversion dynode detector is not as commonly used at the electron multiplier yet it is similar in design where the secondary electrons strike a phosphorus screen instead of a dynode. The phosphorus screen releases photons which are detected by the photomultiplier. One advantage of the conversion dynode is that the photomultiplier tube is sealed in a vacuum, unexposed to the environment of the mass spectrometer and thus the possibility of contamination is removed. This improves the lifetimes of these detectors over electron multipliers.

ARRAY DETECTOR

An array detector is a group of individual detectors aligned in an array format. The array detector, which spatially detects ions according to their different m/z , has been typically used on magnetic sector mass analyzers. Spatially differentiated ions can be detected simultaneously by an array detector. The primary advantage of this approach is that, over a small mass range, scanning is not necessary and therefore sensitivity is improved.

CHARGE (OR INDUCTIVE) DETECTOR

Charge detectors simply recognize a moving charged particle (an ion) through the induction of a current on the plate as the ion moves past. This type of detection is widely used in FTMS to generate an image current of an ion. Detection is independent of ion size and therefore has been used on particles such as whole viruses.^{3-4,30-31}

VACUUM SYSTEM

In order to work in a predictable and efficient way, mass analyzers require high levels of vacuum. so that the analyte ions under investigation must be manageable and sensitive to the electrostatic components of the instrument. Vacuum technology is used to remove the majority of background (air) molecules, as the deflection of ions by the spectrometer on a specific pathway takes place only under the influence of electric, magnetic and/or radiofrequency fields, which would otherwise result in deviation due to collision. The vacuum systems of most recent LC-MS systems consist of a differentially pumped system, typically with a foreline pump establishing a 'rough' vacuum and a high vacuum pump or

pumps located on the analyzer body to establish the high levels of vacuum needed for effective mass to charge ratio measurement. A high level of vacuum within the instrument prevents deviation of the analyte ion from the specified path and assists the processes of ion movement and separation within the following ways:

- By providing an adequate mean free path for the analyte ions.
- By facilitating collision free ion trajectories.
- By the reduction of ion-molecular reactions.
- By minimization of background interference.

EXAMPLES OF VACUUM PUMPS

- Rotary pumps
- Foreline pumps
- Turbo-molecular pumps
- Diffusion pumps³²

CONCLUSION

All mass spectrometers combine ion formation, mass analysis, and ion detection. In its simplest form the process of mass analysis in LC-MS involves the separation or filtration of analyte ions (or fragments of analyte ions), created by various ionization techniques. The mass analyzer is a critical component to the performance of any mass spectrometer. Among the most commonly used are the quadrupole, quadrupole ion trap, time-of-flight, time-of-flight reflectron, and FTMS. However, the list is growing as more specialized analyzers allow for more difficult questions to be addressed. Each mass analyzer has its own special characteristics and applications and its own benefits and limitations. The choice of mass analyzer should be based upon the application, cost, and performance desired. There is no ideal mass analyzer that is good for all applications. Once the ions are separated by the mass analyzer they reach the ion detector, which is ultimately responsible for the signal we observe in the mass spectrum.

CONFLICT OF INTEREST

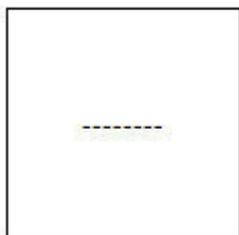
Conflict of interest declared none.

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We sincerely thank the above reviewers for peer reviewing the manuscript