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Review Article

Advances in LC–MS Mass Analyzers: A Comprehensive Review of Quadrupole, TOF, Orbitrap, and Emerging Hybrid Platforms

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ABSTRACT

Liquid chromatography–mass spectrometry (LC-MS) has become a pillar technology in the field of analytical sciences, fuelled by ongoing improvements in mass spectrometer design and performance. The history of LC-MS instrument evolution is reviewed here, highlighting the shift from conventional quadrupole-based instruments to state-of-the-art high-resolution devices like time-of-flight (TOF) and Orbitrap analyzers. This review discusses how these technologies have enhanced analytical performance in terms of sensitivity, mass accuracy, dynamic range, and throughput. Quadrupole devices, with their ruggedness and quantitative accuracy, formed the bedrock for regular analyses, whereas TOF and Orbitrap technologies have made deeper qualitative assessments possible through high-resolution accurate-mass (HRAM) determinations. The combination of hybrid systems, e.g., Q-TOF and Q-Orbitrap, and data collection strategies has further broadened the utility of LC–MS applications in areas from proteomics and metabolomics to environmental and clinical studies. This review points out the major technological advancements in mass analyzers.

Introduction

The origins of LC-MS trace back to the 1950s–1960s, when researchers sought to combine chromatographic separation with the identification power of mass spectrometry. While GC–MS was developed early, LC-MS progressed more slowly because liquid mobile phases were difficult to interface with the high-vacuum environment required by mass spectrometers.[1] One of the first LC-MS interfaces was created in 1968 by Victor Talrose and others in the Union of Soviet Socialist Republics (USSR) with a capillary inlet to couple an LC column to an electron ionization (EI) source.[2] During the 1970s, this method was expanded by McLafferty's group through chemical ionization (CI), and Finnigan researchers developed the moving-belt interface (MBI), which facilitated interfacing LC systems with different ion sources, albeit being laborious and eventually discontinued.[1] The 1980s witnessed a revolution in LC–MS interface technology and ionization methods. Thermospray (TSP), discovered by Vestal and co-workers, became a common interface, facilitating LC flows up to 2 mL/min to be diverted into the mass spectrometer [1]. Fast atom bombardment (FAB) and atmospheric pressure chemical ionization (APCI) also appeared on the scene about this time. The most revolutionary innovation, however, emerged in 1989 with John Fenn's introduction of electrospray ionization (ESI), which enabled the soft ionization of big, non-volatile biomolecules, ushering in protein and peptide analysis. ESI and APCI became the pillars of contemporary LC-MS ionization, supporting compatibility with a wide variety of analytes. By the early 1990s and early 1980s, LC-MS systems were commercially

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available. Sciex launched Atmospheric pressure ionization (API III), a commercial LC-MS instrument supporting both ESI and APCI ionization techniques, in 1989.[3,4] The system set the pace for the popularity of LC–MS application in pharmaceutical analysis, especially for drug metabolism and pharmacokinetics. The advent of triple quadrupole (QqQ) instruments during the early 1990s allowed tandem mass spectrometry (MS/MS), significantly improving selectivity and sensitivity in quantitative uses. TOF and hybrid quadrupole-TOF (Q-TOF) analyzers soon followed, with HRAM information, with Waters introducing one of the initial commercial Q-TOF instruments in 1996. The 2000s saw the advent of high-resolution mass spectrometry. Thermo Fisher's introduction of the Linear Trap Quadrupole Orbitrap (LTQ Orbitrap) in 2005 technology that had been originally patented in Russia, transformed precise mass measurement with unparalleled resolution and dynamic range.[1] Concurrently, technology developments in liquid chromatography, including ultra-high-performance liquid chromatography (LC-UHPLC) and microflow systems, enhanced the speed and sensitivity of separation. With the incorporation of higher ion mobility, advanced data software, and automation, LC–MS emerged as an essential instrument across research fields such as proteomics, metabolomics, food safety, and environmental monitoring.[1,4]

LC separates the sample's components due to their chemical properties, whereas MS identifies and detects them according to their mass-to-charge ratios (m/z).[5,6] LC-MS has changed dramatically, moving from low-resolution quadrupole-based systems to hybrid high-resolution systems. This is based on demands for extensive proteomic/metabolomic coverage, high mass accuracy, and speed. LC–MS is now a workhorse analytical tool in biological and chemical sciences, merging the separation capability of liquid chromatography with the detection capability of mass spectroscopy.[7-9] The coupling of high-resolution mass analyzers like Orbitraps and TOF with new front-end separations has transformed the throughput and Sensitivity of LC-MS processes. Through this development, more comprehensive information is gained regarding biological systems, biomarker discovery becomes feasible, and drug development takes a shorter time.[10,11]

Evolution High-Resolution Mass Analyzers

Early LC–MS instruments used low-resolution quadrupole analyzers, which were economical and sensitive but had low resolving power and mass accuracy. To overcome these limitations, ion trap and TOF analyzers were brought into the market, which provided improved resolution and acquisition rate, significantly improving performance for complex sample analysis.[12,13] The 2005 Orbitrap introduced high precision, resolution, and speed via ion orbital trapping, becoming central to LC-MS proteomics and metabolomics. Successive Thermo Fisher platforms (LTQ Orbitrap, Q Exactive, Fusion, Elite, Exploris) improved resolution, sub-ppm accuracy, and scan rate through the S-lens, high-field Orbitraps, the C-trap, eFT processing, and hybrid quadrupole/ion-trap designs. Quadrupole–Orbitrap systems (e.g., Q Exactive) combine accurate quadrupole precursor selection with Orbitrap high-resolution detection for deep profiling. Advances in MR-TOF with folded flight paths further raised TOF resolution for metabolomic and pharmaceutical work. Hybrid instruments provide CID, HCD, ETD, and support DDA and DIA for flexible, high-depth analysis of complex samples and structural characterization.[14-16]

Classification of Mass Analyzers

Mass analyzers are classified as-

Quadrupole analyzers

- Single quadrupole
- Triple quadrupole

Time-of-flight (TOF) mass analyzers

- Linear TOF
- Reflectron TOF
- Enhanced TOF techniques
- Time-lag or delayed extraction TOF
- Orthogonal acceleration TOF (oa-TOF)
- Multi-reflecting TOF (MR-TOF)/Astral MRT

Orbitrap mass analyzers

FT-ICR

Mass Analyzers

Quadrupole analyzers

The quadrupole mass analyzer was originally suggested in 1953 by Wolfgang Paul and his student at the University of Bonn, Germany, Helmut Steinwedel. Wolfgang Paul, a 1989 Nobel laureate, became known for devising the theory and design of employing four closely spaced parallel rods that produce combined direct current (DC) and radiofrequency (RF) fields to selectively stabilize ion trajectories by their m/z ratio.[17] By 1960, quadrupole mass spectrometers were used as residual gas analyzers, and in 1962 Electronics Associates, Inc. (EAI) marketed the first commercial quadrupole to NASA for vacuum-chamber analysis.[18] Robert E. Finnigan subsequently combined the quadrupole analyzer with gas chromatography and a computer system, and his Finnigan Instruments Corp. introduced the first commercial GC–MS quadrupole system in 1969.[19] Advances such as microprocessor control in the 1970s and the development of QqQ systems later in the decade established the quadrupole as a core tool in modern analytical MS. These innovations made quadrupole instruments compact, affordable, and versatile for applications in environmental testing, pharmaceuticals, proteomics, GC-MS, and other fields. Quadrupole analyzers selectively transmit ions by m/z, enabling reliable identification and quantification of components in complex mixtures.[20]

Design and Construction

A quadrupole mass analyzer is a set of four parallel rods made of metal that are arranged in a square shape, with opposite rods being electrically joined together. A traditional quadrupole mass analyzer uses four cylindrical rods placed symmetrically around an axis in a square pattern.[11,20] The rods, typically 5–12 mm in diameter and 100–200 mm long, are spaced so that the gap between opposing faces is about 1.148 × the rod diameter, approximating an optimal hyperbolic field. An RF voltage with a DC offset is applied to opposing rod pairs, generating oscillating fields that selectively stabilize ions of specific m/z values while destabilizing others, which then strike the rods.[21] A combined RF and DC voltage is applied across the rods, creating an oscillating electric field that steers ions entering along the quadrupole's central axis. Only ions with specific m/z values follow stable trajectories to the detector; all others become unstable and are filtered out. By varying the RF and DC voltages, the quadrupole scans through different m/z values to analyze multiple ions.[22] A schematic representation of a quadrupole mass analyzer is shown in Fig. 1.[23]

Advantages[24]

Quadrupole mass analyzers are valued for their speed, ruggedness, and efficiency, making them ideal for routine work in many laboratories. They rapidly scan m/z ranges to detect multiple sample components. Their moderate resolution is sufficient for most analyses, offering a practical balance between performance and usability compared with higher-resolution systems like TOF or Orbitrap instruments. Quadrupoles are also compact and relatively inexpensive, making them attractive for labs with limited budget or space.

Applications[25]

Environmental monitoring, clinical and pharmaceutical analysis, proteomics and metabolomics, and petrochemical analysis.

Limitations[26]

Lower resolution than other high-resolution mass analyzers, limited mass range, usually up to around 4000 Da for most commercially available instruments, ions are scanned sequentially, hence not for very rapid dynamic processes involving simultaneous detection.

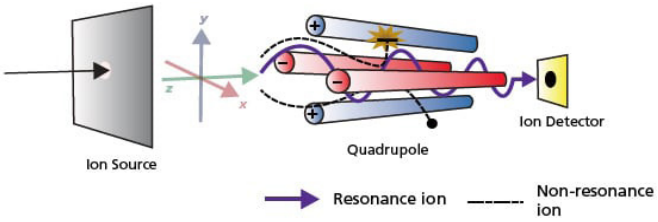

Fig. 1: Schematic representation of Quadrupole Mass Analyzer [25]

Single Quadrupole[14,27-30]

A single quadrupole mass spectrometer (SQMS) is a widely used, reliable, and cost-effective mass analyzer. It consists of four parallel metal rods arranged in a square, with opposite rods electrically paired. A combination of RF and DC voltages, with positive DC on one pair and equal negative DC on the other, both with the same RF, creates an oscillating electric field that filters ions by m/z. Only ions with stable trajectories reach the detector; others are deflected. Scanning is achieved by varying the RF/DC voltages. Key components include an ion source (EI, ESI, APCI), the quadrupole mass filter with unit mass resolution and a detector such as an electron multiplier or Faraday cup.

Applications

Environmental analysis -e.g., pesticide residue monitoring, pharmaceutical quality control -e.g., impurity profiling, Clinical diagnostics - e.g., therapeutic drug monitoring, Food safety- e.g., contaminant detection. Comparison of SQMS with other mass analyzers is illustrated in Table 1.

Advantages

Simple and low-cost compared to MS/MS or high-resolution instruments, good sensitivity for routine quantification, Easy to maintain and operate.

Limitations

Lacks structural information as it has no MS/MS capability, lower selectivity compared to tandem or high-resolution systems, cannot separate isobaric compounds limited resolution.

Triple Quadrupole (QqQ)

The QqQ mass analyzer, a building block of MS/MS, was originally conceived and fabricated in the late 1970s. Based

Table 1: Comparison of SQMS with other mass analyzers

Feature	*SQMS*	*QqQ*	*TOF*
MS/MS capability	No (Single stage)	Yes (Tandem-in-space)	Yes (when coupled)
Resolution	Low (~1000)	Medium (~2000)	High (20k – 100k+)
Cost	Low (>100 ppm)	Medium (50-100ppm)	Excellent (<5 ppm)
Use in quantification	Excellent	Excellent	Good

upon the previous invention of the single quadrupole mass filter by Wolfgang Paul in the 1950s, the triple quadrupole system was brought forth to improve structural elucidation as well as quantitative analysis [31]. The first operational proof was made by SCIEX researchers, led by Dr. Richard Yost and Dr. Chris Enke, in 1978, showing that three successive quadrupoles, as Q1 for precursor ion isolation, Q2 as a collision cell, and Q3 for fragment ion analysis, allowed high selectivity and sensitivity for the detection of target compounds. This innovation impacted the areas of pharmacokinetics, environmental science, and proteomics because it provided a strong quantitation function.[32] QqQ systems employ two mass filters sandwiching a collision cell. This architecture enables multiple reaction monitoring (MRM), providing superb sensitivity and specificity for targeted quantitation in clinical and pharmaceutical applications.[33]

Components and Configuration

Quadrupole 1 (Q1)

It serves as a mass filter and filters precursor ions of a particular m/z ratio from the ion source, which can be scanned to obtain full-scan MS spectra or fixed to transmit a given m/z in selected ion monitoring (SIM).

Quadrupole 2 (q2) – Collision Cell

It serves as a CID cell which filled with an inert gas like argon or nitrogen. Precursor ions get fragmented on collision with gas molecules.

Quadrupole 3 (Q3)

It scans the fragment ions, i.e., Product ions produced by q2. It can be fixed or scanned to monitor particular fragments and facilitates MRM or selected reaction monitoring (SRM). Schematic representation of QqQ is shown in Fig. 2 [34]. Description of operation modes of QqQ is given in Table 2.[35,36]

Applications[37,38]

Pharmacokinetics and drug metabolism studies, clinical diagnostics, e.g., hormone or vitamin D assays, environmental analysis, e.g., pesticide residues, and food safety testing. Proteomics and metabolomics, e.g., targeted metabolite quantification, biomedical research, MRM in

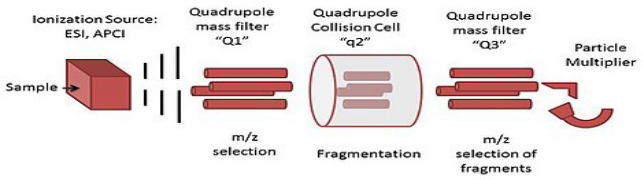

Fig. 2: Schematic Representation of QqQ[37]

Drug Analysis

In pharmacokinetic research, MRM is employed to track individual transitions of a drug molecule and its metabolites.

Advantages[39]

High sensitivity and selectivity, perfect for quantitative analysis, particularly in biological samples. Low limits of detection (LOD), able to analyze complex matrices with little or no sample preparation.

Limitations[40]

Not ideal for untargeted discovery-type studies, needs advanced knowledge of analytes for the development of MRM, Poor resolution when compared with high-resolution instruments such as Orbitrap or TOF.

TOF Analyzers

The TOF mass analyzer boasts a rich and continually developing history that stretches as far back as the early 20th century, with its early principles based on the discoveries of British physicist W.E. Stephens in 1946. Stephens originally suggested the idea of a mass spectrometer in which ions are accelerated through a constant potential and then free to drift through an area free from electric fields, their time of flight to a detector being proportional to the inverse square root of their m/z ratio.[41] Early TOF designs were nevertheless technologically constrained, specifically in ion detector and timing electronics, which limited resolution and precision. Considerable progress was made in the 1980s and 1990s, mostly due to the advent of fast electronics, pulsed ionization methods, and reflectron technology that greatly improved mass resolution by correcting for initial kinetic energy disparities between ions.[42] The interfacing of TOF analyzers with soft ionization methods

Table 2: Operation Modes for QqQ

Mode	*Description*
Full Scan	Q1 and Q3 scan across a range of m/z values
Product Ion Scan	Q1 is set to select precursor ion, Q3 scans product ions.
Precursor Ion Scan	Q3 fixed, Q1 scans to identify all precursors of a certain fragment.
Neutral Loss Scan	Q1 and Q3 scan with constant m/z difference
MRM	Q1 and Q3 are locked on to specific precursor product transitions,

such as matrix-assisted laser desorption/ionization (MALDI) and ESI in the 1990s was a revolutionary period, facilitating high-resolution and high-throughput analysis of macromolecules.[43] TOF analyzers constitute a category of mass spectrometers that distinguish ions on the basis of their m/z ratio by measuring the duration for the ions to cover a known distance. Since their invention in the 1940s, TOF analyzers have made tremendous improvements and are today central to numerous analytical contexts, such as proteomics, metabolomics, environmental analysis, and space exploration, due to ongoing advancements in detector technology and data acquisition hardware.[44]

Principle of Operation

TOF analyzers work on the basic principle that when ions are accelerated by an electric field to a similar kinetic energy, their velocity and therefore their time of flight is a function of their m/z ratio, according to the equation -t=m/2Vq

Where: t = time of flight, V = accelerating voltage, q = charge of the ion, m = mass of the ion.

Light ions move more quickly and reach the detector earlier than heavier ions. When ions are accelerated by an electric field to the same kinetic energy, the lighter ions will go farther than the heavier ions. By precisely measuring their flight time over a known distance, the m/z ratio of the ions can be calculated.[45-47] A TOF analyzer includes an ion source (e.g., EI, ESI, MALDI), an acceleration region that applies high voltage to propel ions, and a drift tube where ions separate by mass in a field-free vacuum. A reflectron may be added to correct kinetic-energy differences and improve resolution. Finally, a fast detector such as an MCP records ion arrival times to determine their m/z values accurately.[47] Schematic representation of TOF is shown in Fig. 3.[48]

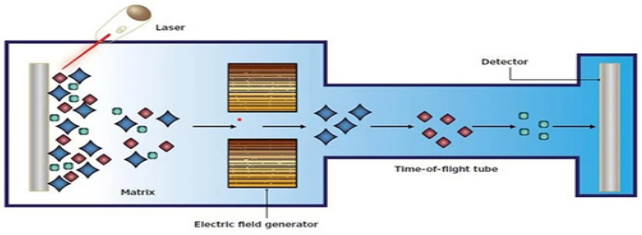

Fig. 3: Schematic Representation of TOF mass analyzer[51]

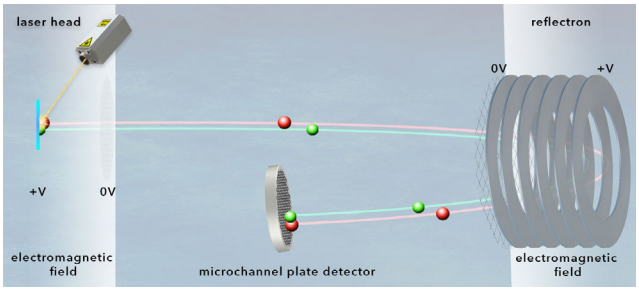

Fig. 4: Schematic Representation of ReTOF Mass Analyzer[53]

Types of TOF Analyzers

Linear TOF

It has a less complex design and ions travel in a straight line from the ion source to the detector after acceleration. Linear TOF offers high sensitivity, ideal for detecting high mass species like proteins and microbes, but suffers from broadening due to kinetic energy dispersion.[49]

Reflectron TOF (Ion Mirror)

The reflector or reflectron was invented by Mamyrin in 1994. In the reflector TOF analyzer, also shortened to ReTOF. The reflector serves as an ion mirror, which concentrates ions with varying kinetic energies in time. ReTOF comprises an ion mirror to compensate for energy spread and enhance resolution. To counteract energy spread and enhance resolution, TOF instruments often incorporate a reflectron, an electrostatic mirror at the end of the tube. As faster ions penetrate deeper, travel faster, and realign with slower ions upon reflection, this reduces time spread. Schematic representation of ReTOF is shown in Fig. 4.[50] Resolution boost of ReTOF effectively doubles the flight path and compensates for energy, improving resolution from a few hundred to tens of thousands.

Two design variants are available for ReTOF:

Single-stage: Simple but limited energy compensation.

Dual-stage/gridless/non-linear field: More complex designs offer superior focus and reduced scattering.[51-53]

Enhanced TOF Techniques

Time-lag or Delayed Extraction

Delayed extraction is the process of applying the extraction electric field once ion formation via laser desorption or other means has taken place for some brief time, typically tens to hundreds of nanoseconds. This delay, prior to acceleration into the TOF analyzer, allows ions to separate in space slightly depending on their original kinetic energies. This adds a delay after ionization prior to application of the acceleration voltage. This aligns ions with different initial energies into a more compact clump, refining the peak.[54.55]

How It Works (Step-by-Step)

Ion formation

Ions are generated in a pulsed ion source, typically through methods such as MALDI.

Free expansion (Delay time)

Ions expand within the ion source prior to acceleration. The more energetic ions travel farther away from the ionization location and the less energetic ions fall behind.

Extraction field applied (Following the delay)

The ions now have slightly different positions. The electric field accelerates them, but due to their varied positions,

the lower-energy ions are subjected to a stronger field for longer periods of time, accelerating them. This accounts for their initial lower energy.

TOF analysis

Following acceleration, ions with the same m/z but varying initial energies reach the detector more closely in tandem, enhancing the temporal focus.[56,57]

Time-lag delayed extraction has key benefits of improved mass resolution, increased sensitivity and reduced mass errors. It is most widely used in MALDI-TOF MS, proteomics and biological studies, as well as polymers and surface analysis.[58-60]

Orthogonal acceleration TOF (oa-TOF)

Bateman and co-workers at Micromass brought OA-TOF as a hybrid analyzer to the scene in the late 1980s/early 1990s. Orthogonal acceleration solved energy spread problems in CID to improve TOF application in tandem MS. Orthogonal Acceleration oa-TOF is an important method employed in time-of-flight mass spectrometry (TOF-MS) to enhance mass resolution and enable continuous ion production and analysis, especially in combination with ion sources such as ESI or MALDI.[61] oa-TOF is a method in which a continuous ion beam is accelerated periodically and perpendicularly into a TOF analyzer. The ion beam is introduced into the system along one axis, usually horizontal. A pulse is applied orthogonally to the ion beam, deflecting and accelerating a thin slice of the ion beam into the TOF drift region. Only ions within the extraction region at the time of the pulse are examined. It is done repeatedly fast, accumulating many little ion packets for analysis.[62] Early OA-TOF instruments, e.g., the 1997 hybrid magnetic sector/OA-TOF, reported mass accuracies of ±10–25 ppm for ions of 200 Da or larger. oa-TOF also facilitates fast acquisition rates and resolving power ~5000 FWHM, perfect for rapid separations such as capillary electrophoresis [63-64].

How OA-TOF Operates (Step by Step)

Ion Generation

A steady-state ion source, e.g., ESI, produces a beam of ions.

Ion Optics

Ions are steered and collapsed into a thin beam by ion optics, e.g., lenses, quadrupoles.

Orthogonal extraction

A pulsed field is applied across the ion beam, perpendicular to it. A thin "slice" of ions is accelerated into the TOF analyzer at regular intervals.

Drift Region

Ions drift in both directions through a field-free region. Lighter ions arrive more quickly at the detector than heavier ones.

Detection

The arrival times are captured quickly by a rapid detector, e.g., a microchannel plate. A time-to-digital converter (TDC) or time-to-analog converter (TAC) digitizes or analogizes the times into m/z data.

Repetition

The orthogonal acceleration is repeated thousands of times every second to provide a thorough analysis.[65] As per the performance considerations oa-TOF has mass accuracy around 1 to 5 ppm, resolving power up to 40,000 or higher, very high acquisition speed with improved duty cycle compared to conventional TOF.[64,66] Orthogonally introduced ions into the flight tube, often used in hybrid instruments like quadrupole-TOF(Q-TOF), MALDI-TOF: MALDI with TOF analysis, very prevalent in biomolecular mass spectrometry.[67]

Advantages[68-69]

High speed

Fast data acquisition, generally in nanoseconds to microseconds per spectrum, high

Mass range

Suitable for large biomolecules, e.g., proteins, polymers. Good sensitivity, especially when coupled with soft ionization methods.

Non-scanning

All ions are sensed simultaneously, allowing fast analysis.

Limitations[67,70]

Mass Resolution is lower than other analyzers like FT-ICR or Orbitrap, although reflectron designs have alleviated this; densely charged ions can cause peak broadening, needs ultra-high vacuum to operate optimally.

Applications

OA-TOF-MS facilitates the identification and quantitation of metabolites from biological samples, which offers important information related to metabolic pathways.[71] In proteomics identification of peptides and proteins by MALDI-TOF or LC-MS with TOF.[45] OA-TOF-MS finds application in conjunction with chromatography (e.g., GC-Q-TOF, LC-Q-TOF) for fast and precise screening of pesticide residues in environmental and food samples.[72]

Quadrupole-TOF (Q-TOF)[73]

Q-TOF mass spectrometry is a hybrid mass spectrometry method that couples a quadrupole mass filter with a TOF analyzer. Coupling these two instruments provides high resolution, mass accuracy, and sensitivity and makes it appropriate for a number of analytical applications such as proteomics, metabolomics, and pharmaceutical research.

How it Works (Step-by-step)

Ionization

Molecules are ionized with a source like ESI or MALDI.

Quadrupole filtering

The initial quadrupole (Q1) serves to filter ions by a specific m/z.

CID

Targeted ions are broken apart in a collision cell (q2), generating daughter ions for structural analysis.

TOF analysis

The fragments are then introduced to the TOF analyzer, where their flight times are recorded. The time of flight is a function of their m/z, and thus their accurate masses can be determined.

Advantages [74-75]

High mass accuracy usually < 5 ppm and high resolving power >30,000 FWHM with rapid acquisition rates**.** Also have MS/MS capability for structural elucidation.

Limitations [74-75]

Expensive and sophisticated instrumentation required, less sensitive than triple quadrupoles for quantitation.

Multi-Reflecting TOF (MR-TOF)/Astral MRT

The MR-TOF mass spectrometer folds ions between two electrostatic mirrors, elongating effective flight paths usually 30 to 100 m, enhancing mass resolution without needing large physical dimensions. In contrast to conventional reflectrons, MR-TOF relies on gridless mirrors and periodic lenses in order to reduce ion losses and preserve beam focus through successive reflections. Advantages are ultra-high resolution up to 200k–1 M, ppb mass accuracy, and separation of fine isotope structures over a wide m/z range with limitations of vacuum complexity, increased TOF per pulse, which impacts on duty cycle, space-charge and ion-loss issues, albeit that newer "lossless" designs reduce many of these.[76]

Select Series™ MRT (Waters)

Waters SELECT SERIES™ MRT is a high-performance mass spectrometer that utilizes MR-TOF technology. It's intended for ultra-high-resolution, exact mass measurement and used mainly in sophisticated analytical applications such as omics, pharmaceutical exploration, and intricate mixture analysis**.** This series generally offers three modes of operation:

MR-TOF mode, which operates in a standard single pass multireflection mode, resolution enhancement mode (REM) with boosted resolution power to > 3000,000 FWHM due to a second pass, which increases pathlength and Diamond Mode for intact proteins having mass >50kDa.[76,77]

Thermo Orbitrap Astral MRT

Thermo Orbitrap Astral MRT is the combination of Orbitrap MS1 and Astral MR-TOF for MS2, with ~30 m multi-reflection flight path and isochronous ion mirrors, which provides resolution ~100,000 at up to 200 Hz scan rates. Radial trap converter technology allows ultra-fast trapping, deep vacuum control, and ~30 m path deliver 100k resolution at high sensitivity, Space charge capacity ~1000, trap efficiency ~60% at 2 ms overhead, and 200 Hz data acquisition. Remains capable of achieving top-down proteomics and high-throughput MS/MS; although some of these limitations still persist, such as MS1 selection efficiency, trap speed.[76,78,79] Comparison of performance characteristics of different TOF analyzers is shown in Table 3.[76,80,81]

Landmark Innovations

- Wiley–McLaren (1955): Developed time-lag focusing to refine arrival times[43]
- Mamyrin (1966): patented reflectron TOF[82]
- Cotter group (1993): Introduced curved field reflectron to correct broad kinetic energy distributions[83]

Orbitrap Mass Analyzer

The Orbitrap mass analyzer is an HRMS instrument that was invented by Alexander Makarov in the early 2000s and later commercialized by Thermo Fisher Scientific. It has since become an integral tool in proteomics, metabolomics, and small molecule analysis as a result of its inherent ability to combine high resolving power, mass accuracy, and sensitivity.[84] The Orbitrap functions through the harmonic electrostatic trapping of ions in orbital motion around a central spindle-shaped electrode. Ions are

Table 3: Comparison of performance characteristics of different TOF analysers

Feature	*Linear TOF*	*Reflectron TOF*	*O-TOF/Q-TOF/MR-TOF*
Resolution	Low (<5,000)	High (10^3–10^5 m/Δm)	Very high (Q-TOF ~30k–50k, MR- TOF >200k)
Mass Range	unlimited (Ideal for intact proteins)	Slightly restricted by reflectron penetration	High (Lower m/z cutoff in Q-traps)
Acquisition Speed	Very fast	Fast, slightly slower	Fast, but path length lengthens cycle time
Sensitivity	High	Slightly lower due to ion losses	Compromised further in MR-TOF
Complexity & Size	Simple, compact	More complex	Very complex; larger footprint

infused tangentially into the Orbitrap, moving around the central electrode while oscillating along the z-axis, i.e., axial direction concurrently. This axial has no dependence on the energy of the ion and is directly proportional to the ion's m/z ratio. These oscillations create an image current on detection electrodes and digitized and converted using an FT to give a mass spectrum.[85]

Instrumentation of Orbitrap Mass Analyzer[86,87]

Spindle-shaped Central Electrode Structure

This is the central component of the Orbitrap analyzer, which is spindle-shaped with a sharp tip and is charged positively. When ions are injected into the orbitrap, they orbit and oscillate around this central electrode in the electrostatic field generated between it and the outer electrode. The oscillations of ions in the z-direction/axial direction are harmonic, i.e., frequency does not depend on initial velocity, and this frequency is directly proportional to their m/z ratio. The oscillation frequency is monitored and mathematically transformed into m/z data through FT.

Barrel-like Outer Electrode

It encircles the central electrode and has the form of a barrel or a split outer electrode. It produces a stable electrostatic field that captures the ions radially but enables them to oscillate axially. These exterior electrodes detect small image currents created by the oscillating ions, which are amplified and digitized and used to create mass spectra.

ESI or MALDI

These are ion sources employed to create ions. ESI creates ions from a solution by subjecting a liquid to a high voltage to generate an aerosol for large biomolecules such as proteins and peptides. MALDI ionizes analytes that are trapped in a crystalline matrix using a laser. Typically employed for imaging or analysis of intricate biological samples. The created ions are directed into the mass spectrometer with the aid of ion optics.

C-trap and HCD Cell

These are situated ahead of the orbitrap and play a vital function in ion handling and fragmentation. C-trap is an S-shaped linear ion trap that rapidly accumulates, stores, and condenses ions prior to injection into the Orbitrap analyzer. It can store ions for a short time, permitting simultaneous injection into the Orbitrap for analysis, enhancing signal quality and resolution. HCD Cell is a collision cell to fragment precursor ions prior to Orbitrap detection. Ions crash into neutral gas such as nitrogen, shattering them into fragments containing structural information from the molecule. Fragment ions are sent to the C-trap and eventually into the Orbitrap to be detected.

High-vacuum system

The whole Orbitrap analyzer runs in ultra-high vacuum, around 10^{-9} mbar or less. A vacuum is required for minimizing ion-gas molecule collisions, which lead to energy loss and destabilize oscillations, providing stable ion motion and accurate frequency detection for good mass measurements.

Hybrid Configurations of Orbitrap Analyzers[88-89]

LTQ orbitrap series (Orbitrap elite)

The Orbitrap Elite by Thermo Fisher Scientific is a big step forward in mass spectrometry, building upon previous Orbitrap models. It's designed to perform better, offering outstanding resolution, sensitivity, and speed. With a resolving power of 240,000 at m/z 400, it ensures precise mass measurements and clear separation of ions with similar m/z values essential for complex analyses like proteomics. One major upgrade is its greatly improved signal-to-noise ratio, providing up to four times better performance than older versions. This enhancement boosts sensitivity and data quality, making it possible to detect low-abundance substances reliably. By combining a linear ion trap with an Orbitrap analyzer, the hybrid design offers flexibility in workflows and allows users to benefit from the strengths of both technologies. Moreover, the Orbitrap Elite supports various fragmentation methods, such as ETD and CID, enabling more in-depth characterization of proteomes and detailed structural analysis.

Orbitrap fusion series

The Orbitrap Fusion and Fusion Lumos are top-notch mass spectrometers that combine three analyzers a quadrupole, ion trap, and Orbitrap on a single platform to boost analytical depth and speed. The quadrupole is great for precisely targeting ions, while the ion trap quickly breaks them down for detailed analysis and high sensitivity. The Orbitrap then measures ions with incredible accuracy and resolution. The Fusion Lumos can achieve a resolution of up to 500,000 at m/z 200, making it perfect for separating closely related compounds with utmost precision. This is crucial for studies like proteomics and metabolomics where overlapping peaks can muddy the results. Plus, the system can scan really fast, handling multiple scan events per cycle for efficient analysis without compromising sensitivity or resolution. It offers a wide range of fragmentation options, such as CID, HCD, ETD, EThcD, and sometimes UVPD, giving detailed structural insights for peptides, proteins, modifications, and variants.

Q Exactive series (Quadrupole-Orbitrap)

The Q Exactive series of mass spectrometers uses a mix of filters to offer top-notch performance in a compact, user-friendly package. Unlike fancier systems such as the Orbitrap Fusion, the Q Exactive focuses on being easy to use while still delivering great analysis. With models like the Q Exactive, Q Exactive Plus, Q Exactive HF, HF-X, and Q Exactive UHMR, you can tackle a wide range of tasks from identifying small molecules to analyzing intact proteins and complex substances.

Orbitrap exploris series

The Orbitrap Exploris Series is the latest benchtop mass spectrometry family known for its high-throughput and robust analytical capabilities, especially in proteomics research. Within this innovative range, you'll find flagship models like Orbitrap Exploris 120, 240, and 480, each tailored to meet different analytical needs with impressive precision. These systems offer exceptional resolving power ranging from 120,000 to 480,000 at m/z 200, delivering unmatched clarity and detail for analyzing complex samples.

FT-ICR: Benchmark for Ultra High Resolution

FT-ICR mass spectrometry is the gold standard for ultra-high-resolution mass analysis, offering resolving power above 1,000,000 FWHM and sub-ppm to ppb-level mass accuracy. This capability allows precise separation of ions with very similar m/z values, making FT-ICR ideal for highly complex mixtures such as crude oil, environmental dissolved organic matter, proteomes, and metabolomics samples. It supports exact molecular-formula assignment and discrimination among thousands of isobaric species, enabling detailed compositional analysis in fields like petroleomics and top-down proteomics. FT-ICR operates by trapping ions in a strong magnetic field, inducing cyclotron motion, and converting the resulting image currents into mass spectra via Fourier transformation. Despite its unmatched analytical performance, FT-ICR has significant limitations: extremely high capital and operating costs, dependence on cryogenically cooled superconducting magnets, and substantial infrastructure needs, including vibration-free environments and specialized laboratory space. Its operation requires expert personnel for tuning, calibration, and data interpretation, and acquisition times can be longer than those of Orbitrap or TOF systems. Thus, while FT-ICR surpasses Orbitrap and TOF instruments in detail and precision, it is less accessible, more expensive, and slower. Consequently, FT-ICR is best suited for specialized laboratories where maximum analytical detail justifies the complexity and cost.[90-95]

Comparative Analysis

Mass spectrometers employ various kinds of mass analyzers, each with trade-offs among throughput, resolution, mass accuracy, dynamic range, and expense. TOFs and Q Orbitraps provide speed, but resolution is different. TOFs have high throughput, while Orbitraps have high precision. As per the trade-offs, Orbitrap resolution can fall off at high m/z, and so some users prefer TOF for intact proteins.[96] The choice of mass analyzer is a "fit for purpose" decision based on the balance of resolution, speed, and sensitivity. Quadrupoles (SQ/QqQ) are the current gold standard for targeted quantification in the pharmaceutical and environmental industries due to their high linear dynamic range and robustness, although resolution is limited to unit mass resolution of approximately 1,000 FWHM. In contrast, Time-of-Flight and Orbitrap mass spectrometers provide the high-resolution, accurate mass spectra required for discovery-oriented research. Time-of-Flight mass spectrometers, especially the latest generation of Multi-Reflecting Time-of-Flight mass spectrometers, have the very high acquisition speeds required for fast chromatography techniques. In proteomics, Orbitraps are the preferred choice for their excellent mass accuracy <1 ppm and resolving power up to 500,000.[97] At the pinnacle of mass spectrometry instrumentation, Fourier Transform Ion Cyclotron Resonance mass spectrometry provides unparalleled resolving power >1,000,000, essential for identifying subtle isotopic patterns in complex "petroleomic" mixtures, although this comes at a price. In conclusion, although Quadrupoles are the preferred choice for routine applications, the latest generation of Hybrid mass spectrometers, such as the Orbitrap Astral and the Q-TOF, are pushing the boundaries of high-throughput omics and structural characterization.[98]

Future Directions and Challenges[99,100]

The latest advancements in Orbitrap mass spectrometry have continued to concentrate on improving performance while retaining, or even enhancing, resolution. One of the innovations has been speeding up scan speed with instruments such as the Thermo Scientific Exploris family, which takes advantage of sophisticated Automatic Gain Control (AGC) to ensure consistency of ion population and maximize resolution even at increased acquisition rates. This is useful for high-throughput applications as well as real-time analyses. In addition, the fusion of ion mobility spectrometry (IMS), Orbitrap, and TOF technologies, together with artificial intelligence-driven data analytics, is defining a new age of intelligent molecular recognition. The hybrid platforms allow for the acquisition of multidimensional data sets, which improve selectivity and sensitivity over complex samples. Concurrently, there is a greater focus on enhancing the capabilities of native MS, especially to investigate protein complexes in their native forms. Advances in mass-range scaling and soft fragmentation methods are enhancing the amenability of native MS instruments, enabling researchers to interrogate intact macromolecular complexes at higher resolution and versatility. Another notable frontier is the design of space-mission, miniaturized Orbitrap instruments such as the Cosm-Orbitrap for extraterrestrial exploration and remote field analysis. The design brings together high resolution with ruggedized, compact form factors, enabling high-accuracy mass spectrometry in hostile environments off the planet. Lastly, with the development of Orbitrap technology, its cost-performance ratio has become more and more favorable. The new Orbitraps are now comparable in mass accuracy and resolving power to FT-ICR instruments, yet are more user-friendly and less infrastructurally and operationally demanding. This

renders Orbitrap-based platforms an appealing option for both state-of-the-art research as well as everyday analytical procedures.

Conclusion

The evolution of LC-MS mass analyzers has transitioned from foundational scanning quadrupoles to ultra-high-resolution platforms capable of mapping complex biological systems. While triple quadrupole (QqQ) systems remain the "gold standard" for targeted quantification due to their robustness and sensitivity, the advent of Orbitrap and Multi-Reflecting TOF (MR-TOF) technologies has redefined the boundaries of discovery-based research. Modern hybrid platforms, such as the Orbitrap Astral, now bridge the gap between high-speed acquisition and elite mass accuracy (<1 ppm), enabling high-throughput "omic" analysis. Ultimately, the selection of a mass analyzer is a fit-for-purpose decision: QqQ for routine monitoring, and HRAM systems like Orbitrap or FT-ICR for deep structural characterization and untargeted screening.

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