Technical Overview

Ion optics innovations for increased sensitivity in hybrid MS systems

Abstract

Sensitivity, mass resolution, scan speed, spectral fidelity, mass accuracy, and mass range are just a few of the parameters that are used to gauge the performance of a mass spectrometer. While exactly which of these parameters is most important to the instrument user can vary by application, sensitivity is almost always of great interest since sensitivity determines the limit of detection. This overview describes shared ion optics design features that are key to achieving outstanding sensitivity in the Agilent Technologies 6400 Series Triple Quadrupole and 6500 Series Quadrupole Time-of-Flight LC/MS systems. It also describes unique design features that contribute to sensitivity of the individual systems.

Agilent Technologies

Introduction

Maximum sensitivity is not achieved by the performance of any single mass spectrometer component, but results from the interaction of many components. It requires:

- Maximizing ion generation while simultaneously minimizing the generation of noise
- Efficient ion transmission and mass filtering with as little ion loss as possible
- Efficient ion detection that simultaneously reduces or eliminates signal from non-ion sources (either chemical or electronic)

The ion optics of Agilent triple quadrupole and quadrupole time-of-flight (Q-TOF) systems are shown in Figure 1. The major differences between the two instruments are in those components that come after the collision cell and are associated with the second mass filter and detector.

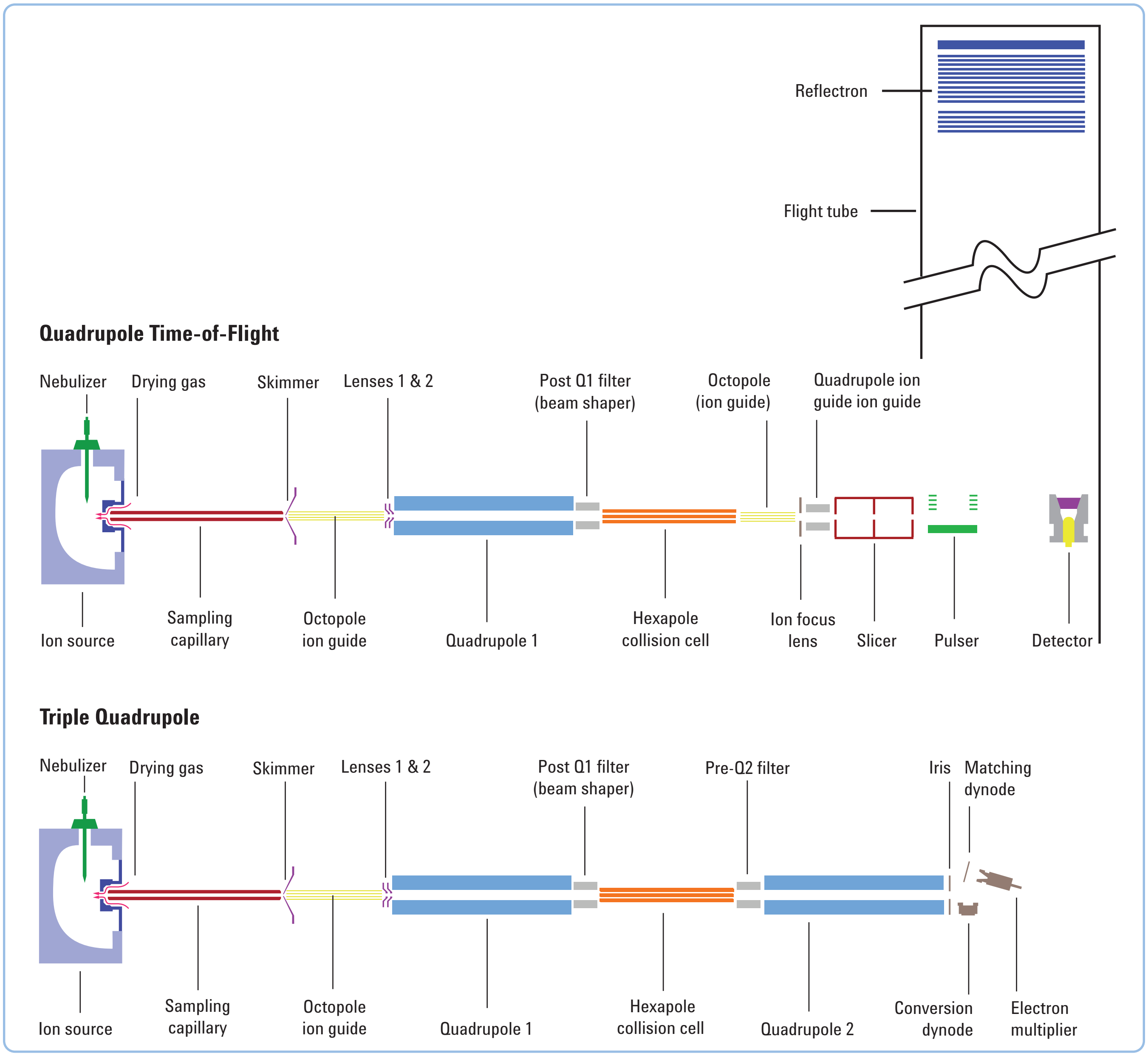

Figure 1. Q-TOF (top) and triple quadrupole (bottom) share most ion optics components up through the collision cell. This reduces the number of variables in multi-instrument research. They differ in the components associated with the second mass filter and detector.

Electrospray ionization source

The first critical component in determining the sensitivity of the triple quad and Q-TOF is the electrospray ionization (ESI) source. The primary design goal of the ion source is to maximize the number of ions produced by the ESI technique while minimizing the generation of neutral particles and high-energy ion clusters that cause noise. Figure 2 shows the orthogonal design of the patented Agilent ESI source. The source incorporates many design features to improve the ion transmission while minimizing the noise that is generally associated with atmospheric pressure ionization.

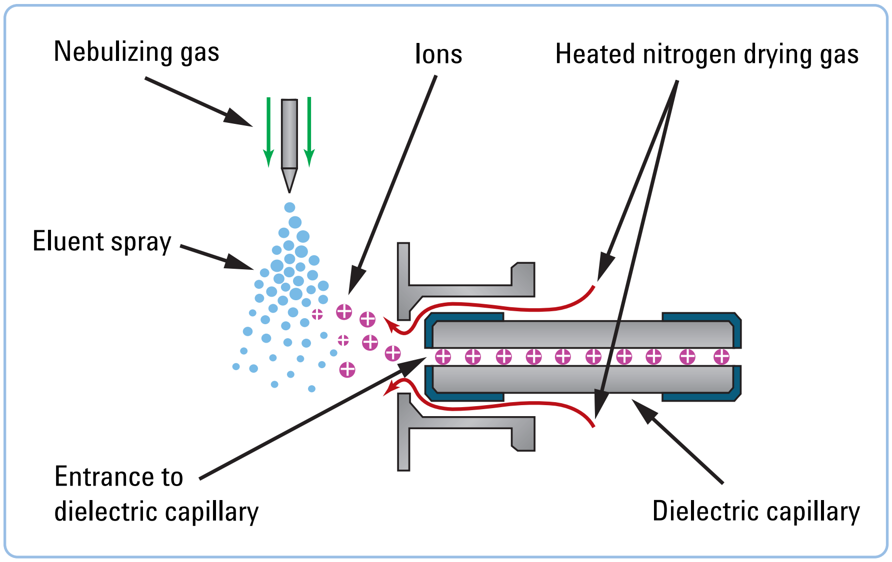

Figure 2. Electrospray ion source is designed to maximize ion generation while minimizing the amount of chemical noise generated and transmitted into the vacuum system.

Generation of small, uniform droplets

The patented mechanical centering design of the ESI nebulizer uses a sheath of nitrogen flowing concentric to the LC effluent to produce droplets. A converging nozzle mechanism accelerates the nebulizing gas. The resulting high velocity and uniform flow of nitrogen produces smaller, more uniform droplets. Smaller, more uniform droplets desolvate in a more consistent manner, ultimately delivering more ions into the instrument and increasing the signal strength.

Orthogonal nebulization

The ESI nebulizer is oriented orthogonally to axis of the dielectric sampling capillary. The orthogonal orientation greatly reduces the number of neutral particles entering the mass spectrometer, thus eliminating noise that would otherwise be generated by those particles. This improves the ultimate signal-to-noise ratio of the instrument.

Heated drying gas

A counter current of heated nitrogen drying gas effectively desolvates the ions formed in the ESI spray. By desolvating the ions in the ion source before they enter the sampling capillary, the drying gas significantly reduces the amount of solvent vapor entering the capillary. Ultimately, this increase signal strength and reduces the number of solvent-adduct ions.

Dielectric sampling capillary

The 6400 and 6500 Series LC/MS systems use a dielectric sampling capillary to convey ions from atmospheric pressure in the ESI source to the vacuum region inside the mass spectrometer. Because a substantial pressure drop (~3X) occurs gradually over the entire length of the capillary, expansive cooling of the ions upon their exit from the capillary is reduced. This significantly reduces the formation of adduct ions.

By contrast, in mass spectrometers that use an orifice or series of orifices instead of a long capillary, pressure reduction often occurs more abruptly with greater expansive cooling. This can result in formation of solvent clusters (sovlent adducts) and generation of matrix ions significantly above the molecular weight of the analytes.

Heated, counter-current drying gas in the ion source also makes it possible for the 6400 and 6500 Series LC/MS systems to use a sampling capillary that is only indirectly heated. LC/MS systems that do not feature heated drying gas often use directly heated, high-temperature capillaries to accomplish desolvation. High temperature capillaries are prone to contamination, and without prior reduction of solvent load by the drying gas, they also tend to produce more solvent adducts.

The Agilent dielectric sampling capillary carries a high voltage at its entrance and a low voltage at its exit. This allows the ESI nebulizer to be grounded, eliminating any chance of high-voltage discharge from the nebulizer to personnel using the mass spectrometer.

Skimmer

Ions exit the capillary with substantial momentum. Beyond the exit of the capillary is a skimmer (Figure 3) that helps maximize ion transmission while minimizing the transmission of neutral gas molecules. Heavier sample ions pass through the skimmer while lighter, neutral gas molecules are pumped away by the vacuum system. The skimmer angle, hole size, position, and distance from the exit of the capillary have been carefully balanced and optimized to achieve maximum ion transmission.

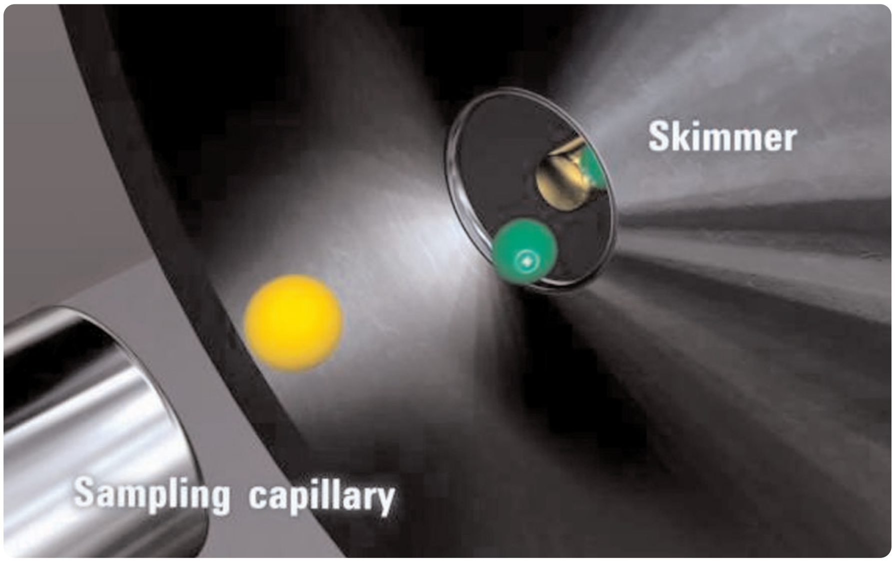

Figure 3. The skimmer angle, hole size, position, and distance from the exit of the capillary have been carefully balanced and optimized to achieve maximum ion transmission.

Octopole ion guide

An octopole ion guide (Figure 4) helps maintain a high degree of ion transmission as pressure is reduced from ~1 Torr to ~10^{-4} Torr by a split-flow turbomolecular pump. Four-, six- or eight-rod ion guide assemblies can be used to perform this function. An eight-rod ion guide was chosen because it requires lower operating voltages than a four- or six-rod ion guide, and because it is more efficient at transmitting ions over a broad range of masses. A 5 MHz RF drive frequency applied to the octopole rods contributes to the broad mass-transmission range.

Lenses 1 and 2

The electrical fields generated by lenses 1 and 2 (Figure 5) optimize transmission of ions from the octopole ion guide into the first mass filter (Q1). Lens 1, carrying a DC voltage, shields the octopole ion guide from effects of the DC and RF voltages on lens 2. The DC voltage on lens 2 accelerates the ions. The RF voltage applied to lens 2 matches the phase angle and amplitude of the RF voltage on the quadrupole to improve acceptance of ions into the quadrupole. The voltages applied to lens 2 increase ion transmission by approximately 2.5 times for ions with *m/z* greater than 600 and 5 times for ions with *m/z* greater than 1500 (Figure 6) compared to the same system without these voltages.

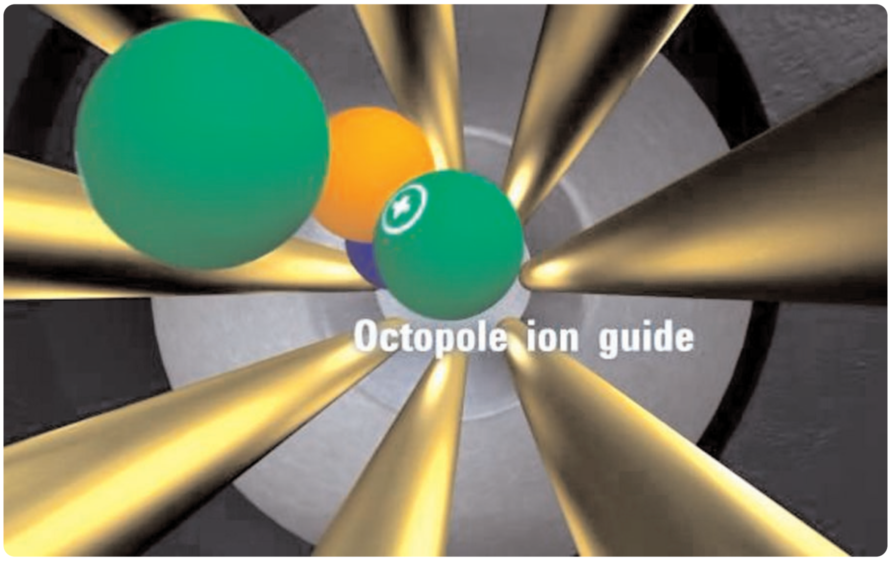

Figure 4. The eight-rod ion guide requires lower operating voltages than a four- or six-rod ion guide and more efficiently transmits ions over a broad range of masses.

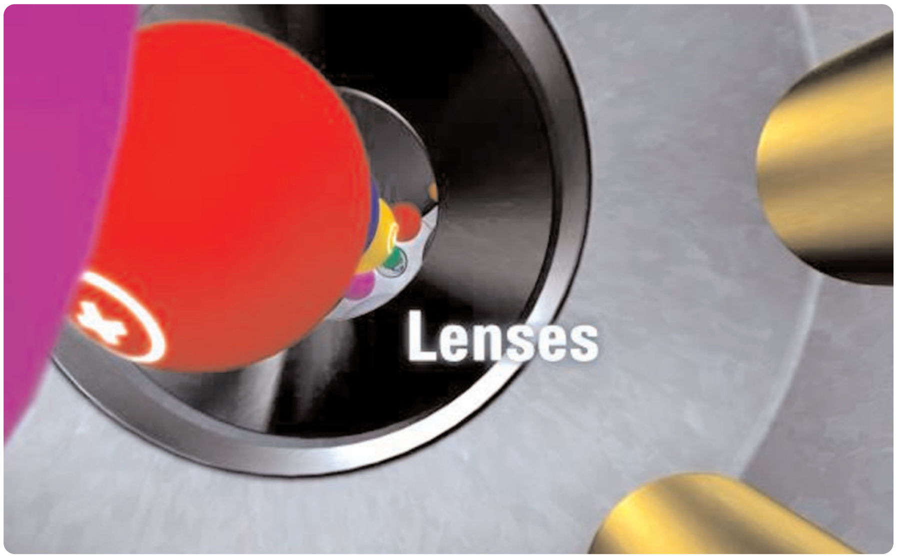

Figure 5. Lenses 1 and 2 optimize transmission of ions from the octopole ion guide to the first mass filter (Q1).

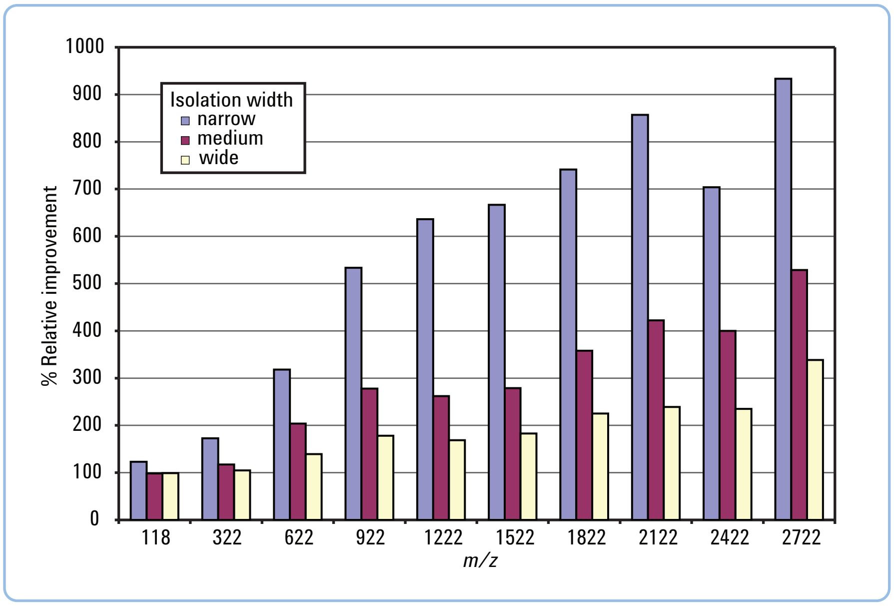

Figure 6. **Compared to the same system without the lens 2 RF, a system with it can increase ion transmission by 2.5 times for ions with *m/z* greater than 600 and by 5 times for ions with *m/z* greater than 1500.**

Quadrupole mass filters

The 6400 Series triple quadrupole LC/MS systems feature two quadrupole mass filters. The 6500 Series Q-TOF LC/MS systems use a single quadrupole mass filter in combination with a time-of-flight mass filter.

Quadrupole design requires the balancing multiple parameters to optimize ion throughput, mass filtering and, in some instruments, ion polarity switching. The quadrupole mass filters used in the 6400 Series and 6500 Series LC/MS systems are composed of four eight-inch hyperbolic rods made from 440C stainless steel alloy. During manufacturing, the rods are positioned to a precision of better than 1 micron and then locked into alignment.

Ion throughput in a quadrupole mass filter (Figure 7) is greatly affected by spacing between opposite rods. This spacing is known as the 2R0 (two R zero) spacing. Wider 2R0 spacing improves ion acceptance and transmission. However, the wider the 2R0 spacing, the greater the voltages that must be applied to the rods to achieve the proper mass filtering. Among other consequences, higher voltages make it harder to quickly switch ion polarity. The quadrupole mass filters in the 6400 Series and 6500 Series LC/MS system have a 2R0 of 8.89 mm. The hyperbolic shape of the quadrupole rods extends the hyperbolic area of the electrical fields—the area in which the ions are transmitted—all the way to the rods. This results in a larger "effective" 2R0 without the voltage and polarity switching disadvantages of a physically larger 2R0 spacing.

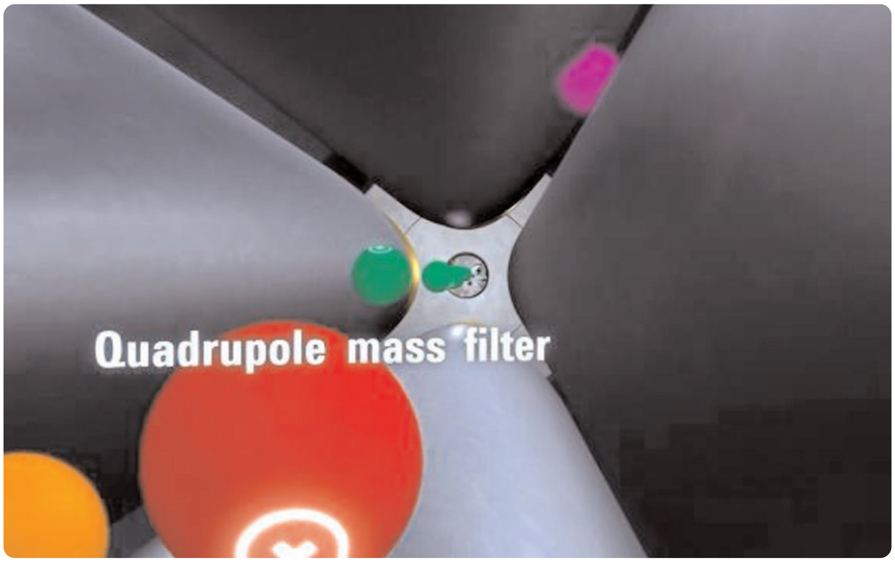

Figure 7. **The spacing between opposite quadrupole rods—called 2R0—has a significant influence on ion throughput. The hyperbolic shape of the rods in the Agilent quadrupoles creates a larger effective 2R0 without incurring the disadvantages of a physically larger 2R0.**

Post-Q1 filter

The post-Q1 filter (Figure 8), also called the beam shaper, is a radio-frequency (RF) ion guide that is capacitively coupled to Q1. It focuses the ion beam and guides the ions into the high-pressure collision cell, ensuring that as many ions as possible enter the collision cell. The filter helps counter the effects of the flow of collision gas that is exiting the collision cell.

Collision cell

The collision cell (Figure 9) is a hexapole assembly. Nitrogen or argon collision gas (user's choice) is gently admitted into the cell at approximately 0.5 mL/min to avoid turbulence that could affect ion transmission. The collision cell operates at a relatively high pressure, which helps eliminate noise by reducing the number of excited neutrals and clusters that are transmitted through the cell by collisions that occur in the cell.

Triple Quadrupole

In early mass spectrometers that employed two quadrupole mass filters, the collision cell between them was frequently also a quadrupole. Thus, this type of hyphenated mass spectrometer was called a triple quadrupole mass spectrometer. The name became somewhat traditional and is frequently used for any mass spectrometer that uses a quadrupole mass filter → collision cell → quadrupole mass filter configuration, even if the collision cell is not a quadrupole.

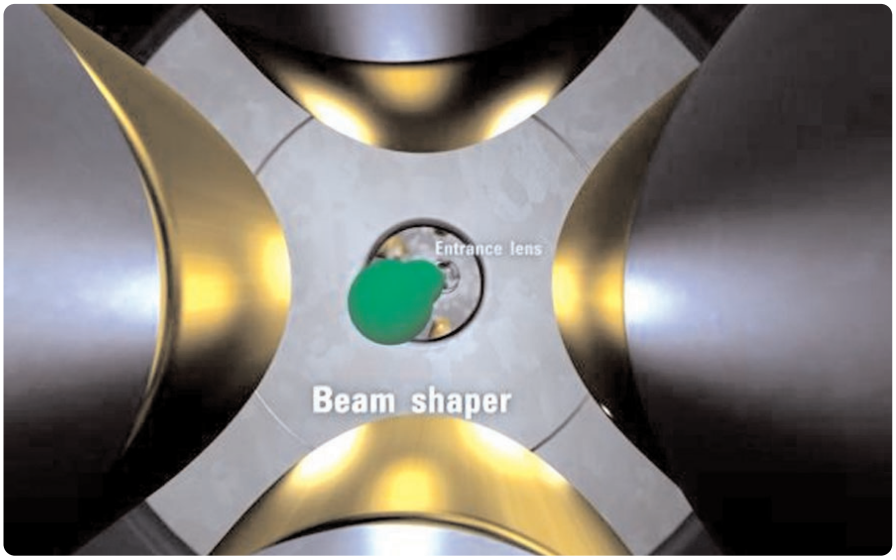

Figure 8. The post-Q1 filter (beam shaper) improves transmission of ions from the quadrupole mass filter to the collision cell.

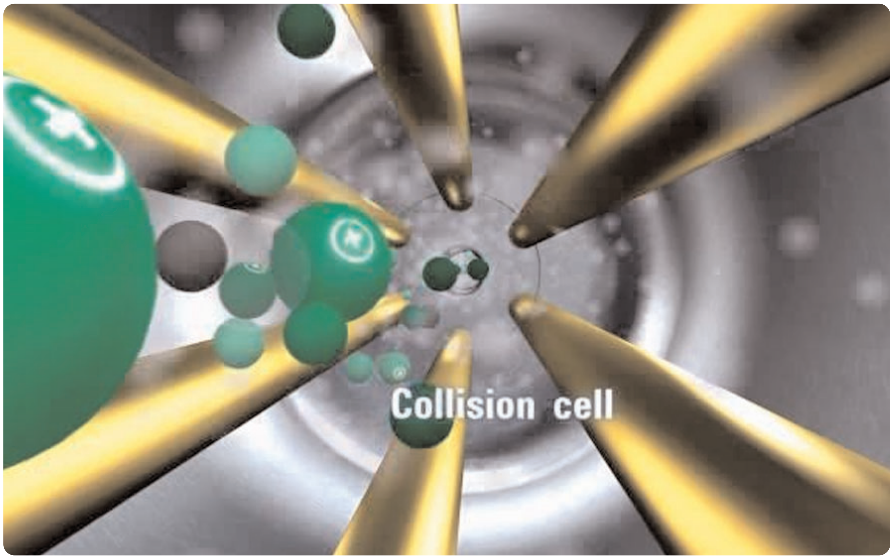

Figure 9. Linear axial acceleration in the octopole collision cell facilitates the use of higher collision gas pressure and reduces carryover that could cause cross-experiment memory effects.

To avoid ion stall out, a negative consequence of a high collision gas pressure, a voltage potential is applied along the length of the resistively coated hexapole rods. This creates linear axial acceleration that maintains ion momentum. This allows more MRM experiments to be performed in a given time, and reduces cross-experiment memory effects due to ion latency.

The energy of the ions entering the collision cell, the collision gas pressure, and the linear voltage gradient are balanced so that ions of all masses exit the collision cell with a negligible (almost 0 eV), but nearly uniform energy. In the case of the Q-TOF instruments, this allows the same mass calibration factors to be applied to MS and MS/MS ions. The result is better than 5-ppm mass accuracy for MS/MS ions.

Components exclusive to triple quadrupole

Pre-Q2 filter

Similar to the post-Q1 filter, the pre-Q2 filter (Figure 10) is a radio-frequency (RF) ion guide that is capacitively coupled to the second quadrupole mass filter (Q2). Its transmit ions from the collision cell to Q2 with minimum loss while allowing the vacuum system to pump away neutral collision gas molecules exiting the collision cell.

Quadrupole mass filter 2

In the 6400 Series triple quadrupole LC/MS systems, the second quadrupole mass filter (Q2) is identical to the first (Figure 10). It uses hyperbolic rods to increase the effective 2R0 and maximize ion throughput, and hence sensitivity, without incurring the voltage and polarity switching disadvantages of a physically larger 2R0 spacing.

Ion detection system

The triple quadrupole LC/MS systems employ a high-energy-dynode electron multiplier for ion detection (Figure 11). Ions first pass through an iris lens whose voltage is ramped according to the mass to improve focusing of ions into the detector.

The detector incorporates two dynodes that improve the ion-to-electron yield. In positive mode, the conversion (primary) dynode operates at –10 KV. Positive ions impact the conversion dynode and generate secondary electrons. These electrons are then attracted to the –1.5 KV matching (secondary) dynode.

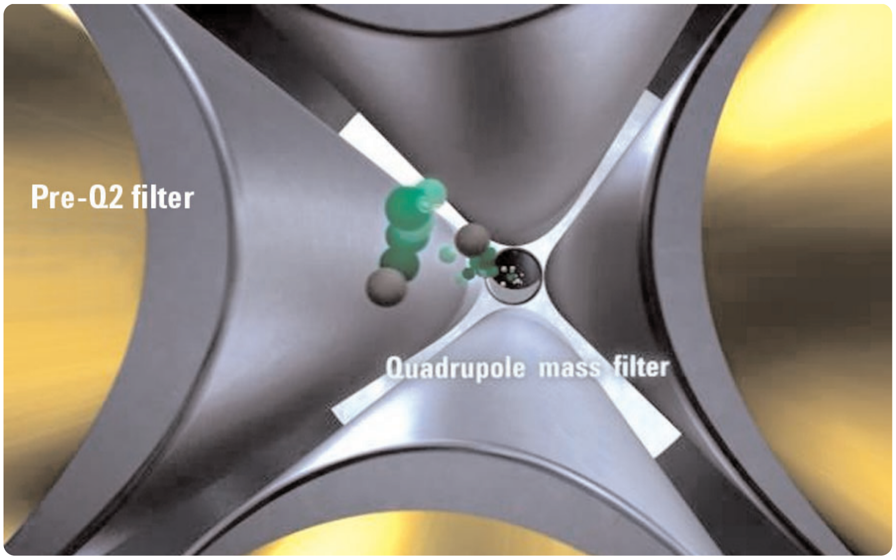

Figure 10. **In the triple quadrupole, the second quadrupole mass filter is identical to the first. It uses hyperbolic rods to maximize ion throughput, and hence sensitivity.**

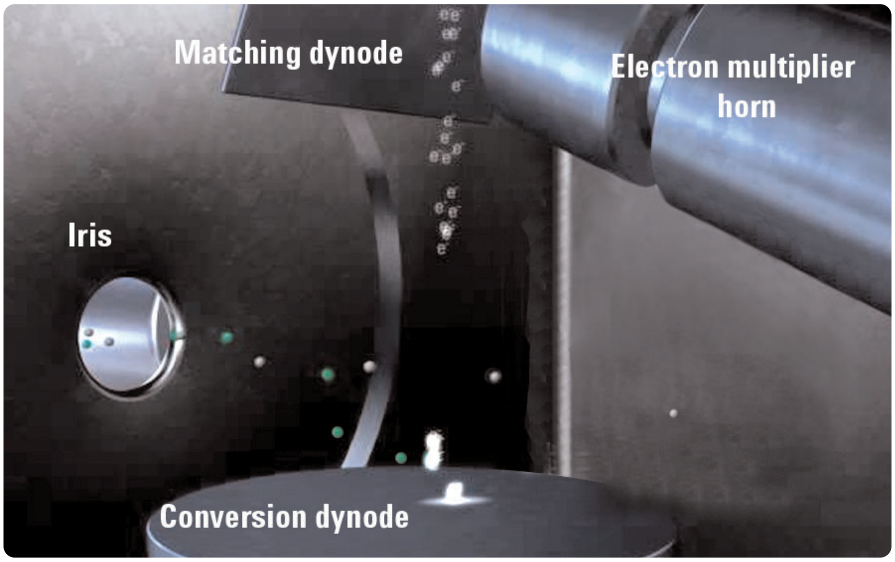

Figure 11. **The triple quadrupole detector is a continuous dynode electron multiplier. Since the conversion dynode, matching dynode, and electron multiplier horn are all off axis, neutral molecules miss the detector, eliminating neutral noise.**

Additional electrons are generated and cascade into the electron multiplier. Since the high-energy conversion dynode, matching dynode, and electron multiplier are all off the main axis of the ion path, neutral molecules miss the detector, eliminating neutral noise. This allows the detector to operate at higher gains for a greater signal without simultaneously increasing noise. A typical gain for the entire detection system is 10^6 to 10^7.

In negative ion mode, the conversion dynode operates at +10 kV. Negative ions impact the conversion dynode, producing secondary positive ions. These positive ions are attracted to the matching dynode at –1.5 kV. They impact the matching dynode and produce secondary electrons. These electrons are then directed to the electron multiplier. Gain characteristics are similar to those for positive ions.

Detection electronics

The electron multiplier current is sampled using an analog-to-digital converter with a logarithmic (log) amplifier. The log amplifier and the rest of the electronics are specifically designed to minimize electronic noise.

Components exclusive to Q-TOF

Octopole ion guide 2

Instead of the pre-Q2 filter in triple quadrupole instruments, the Q-TOF instruments have a second octopole ion guide almost identical to the first (Figure 12). This second octopole ion guide maintains maximum ion transmission while neutral collision gas escaping the collision cell is pumped away by the vacuum system. This is essential since the time-of-flight mass filter requires a lower pressure for optimum operation than does a quadrupole mass filter.

After the collision cell, the Q-TOF vacuum system differs significantly from the vacuum system in the triple quadrupole. Its higher pumping capacity maintains the lower pressure required by a TOF mass analyzer. The Q-TOF vacuum system uses two split-flow turbomolecular pumps to obtain the 10^{-7} Torr pressure required for TOF operation.

Ion focus lens

The ion focus lens (Figure 12) is a round, flat lens with a DC voltage applied to it. This voltage reaccelerates the ions, whose velocities are minimal after exiting the collision cell.

Quadrupole ion guide

The quadrupole ion guide (Figure 12) is a 20-mm section of quadrupole. Different voltages are applied to the two opposing rod pairs. The resulting electromagnetic fields reduce the velocity in the vertical axis and flatten the ion beam to better match it to the shape of the entrance slit in the slicer.

Slicer

The slicer (Figure 13) is a series of horizontal slits that prevent ions with excess velocity in the vertical axis from reaching the time-of-flight mass analyzer. By eliminating ions with excess vertical velocity, the quadrupole ion guide and slicer improve mass accuracy and especially resolving power (better than 20,000 at m/z 1,500).

Time-of-flight mass analyzer

The 6500 Series Q-TOF LC/MS systems employ a time-of-flight (TOF) mass analyzer as the second mass analyzer. A TOF mass analyzer delivers a higher percentage of ions over its complete mass range to its detector than most other types of mass analyzers. This translates to better sensitivity when "full scan" spectra are needed. The TOF mass analyzer in the 6500 Series uses orthogonal acceleration and a two-stage ion mirror (reflectron).

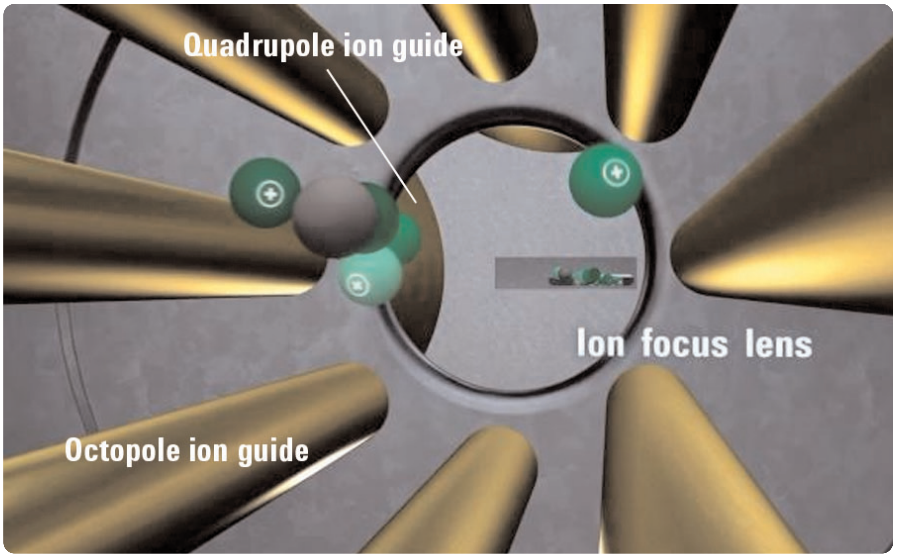

Figure 12. In the Q-TOF instruments, the post-collision-cell ion optics help with removal of the collision gas, shape the ion beam, and eliminate ions with non-uniform vertical velocity to improve the mass accuracy and mass resolution of the time-of-flight mass filter.

Pulser

Pulsed acceleration orthogonal to the axis of the ion source and ion optics (Figure 14) is particularly advantageous for systems that generate a continuous beam of ions. It provides a very precise start to the flight time and, with the quadrupole ion guide and slicer, a much narrower range of initial energies in the ions. The result is better mass resolution and mass accuracy. 6500 Series Q-TOFs uses pulsed orthogonal acceleration at default frequency of approximately 14 KHz (mass range dependent) to deliver as many ions to the detector as possible.

Ion mirror

Ion mirrors improve mass resolution while allowing a smaller instrument due to the folded flight path. The 6500 Series uses a two-stage ion mirror, also called a reflectron, with a “harp” design that improves resolution and sensitivity. The ion mirror self-compensates for thermal changes.

Low-expansion flight tube

The flight tube is constructed from a metal alloy with an extremely low coefficient of thermal expansion in the operating temperature range of the Q-TOF. This minimizes changes in flight distance due to changes in laboratory temperature and helps maintain the instrument’s superlative mass accuracy.

Detector

The QTOF detection system uses a microchannel-plate detector (Figure 15). The ion beam strikes the microchannel plate and generates a stream of electrons. The electrons strike a scintillator,

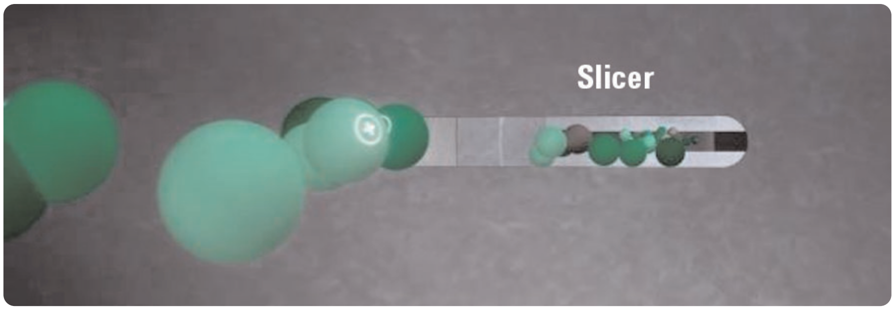

Figure 13. The slicer prevents ions with non-uniform velocity in the vertical axis from reaching the time-of-flight mass filter. This improves mass accuracy and resolving power.

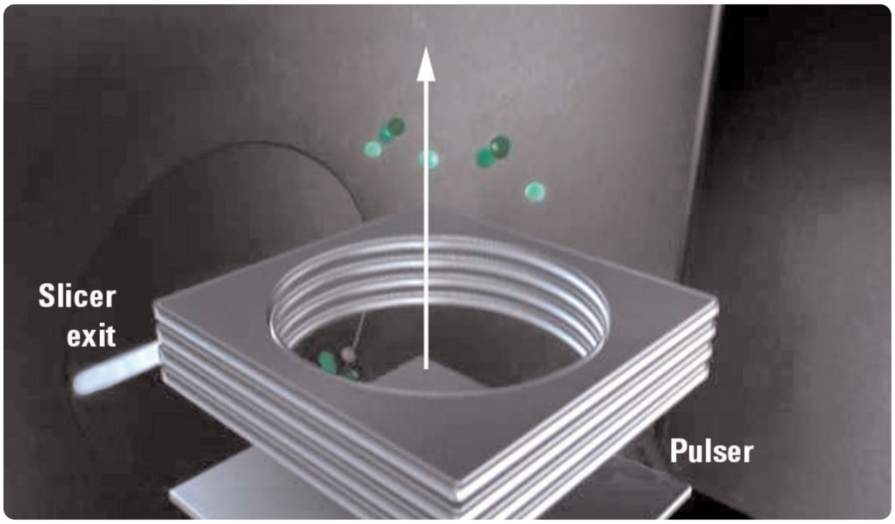

Figure 14. When combined with the quadrupole ion guide and slicer, pulsed acceleration orthogonal to the major axis of the ion optics results in better mass resolution and mass accuracy.

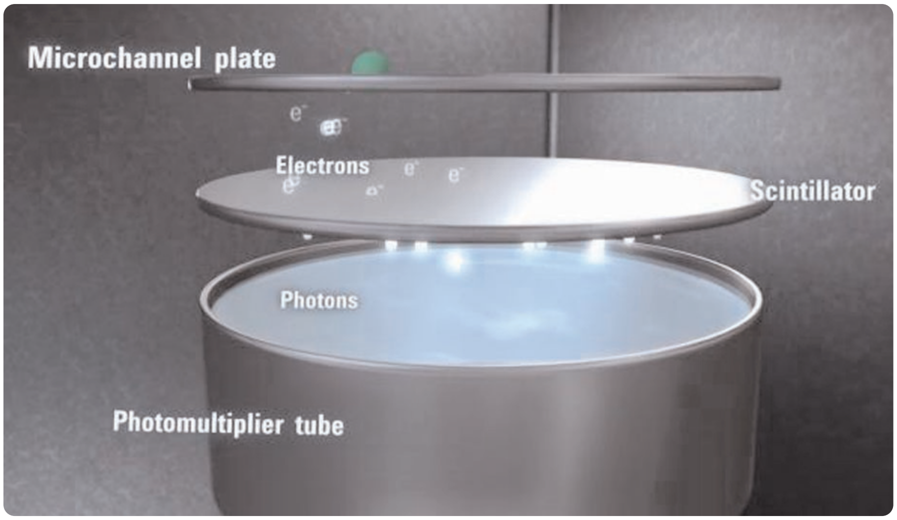

Figure 15. The Q-TOF uses a microchannel-plate detector that provides high gain and low noise for better sensitivity. The Q-TOF detection system also features a wide dynamic range.

producing photos. The photons strike a photomultiplier tube, generating an amplified signal proportional to ion flux. The photomultiplier features high gain with low noise. Because it is isolated from the ions, it also has a long lifespan The dynamic range of the detection system is greater than 10^4.

Detector electronics

Similar to the triple quadrupole systems, the Q-TOF uses an analog-to-digital-conversion (ADC) -based detection system. An analog sampling system avoids many of the ion current saturation and mass assignment inaccuracies associated with a time-to-digital (TDC) detector systems.[1] The detector signal is sampled at a 4 GHz frequency (32 Gbit/sec). This high sampling rate improves the resolution, mass accuracy and accurate abundance measurement of the TOF, especially at lower masses since the low-mass ions are traveling at greater velocities and require more frequent sampling for accuracy.

Conclusion

Maximizing sensitivity in a mass spectrometer requires optimizing the generation, transmission, and detection of ions while simultaneously minimizing the generation, transmission, and detection of chemical and electronic noise. In Agilent 6400 Series Triple Quadrupole LC/MS systems and Agilent 6500 Series Q-TOF LC/MS systems, the entire ion path has been designed with these requirements in mind—from ion generation in the ion source, through ion fragmentation and mass filtering, to ion detection and signal processing. The result is instruments that achieve superlative sensitivity performance without sacrificing other aspects of MS performance (Figures 16 and 17).

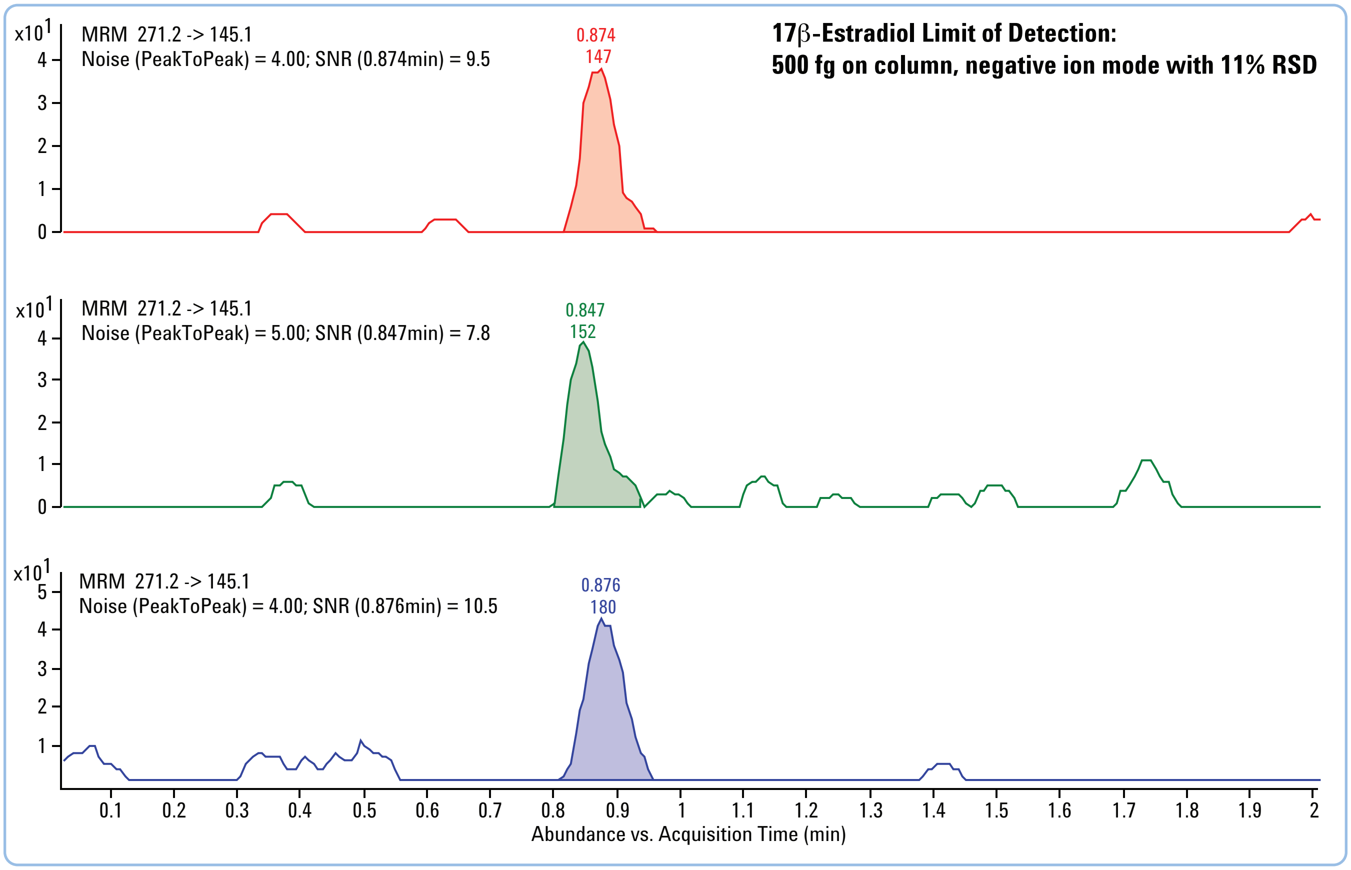

Figure 16. Analysis of 17β-estradiol using the 6410 Triple Quadrupole LC/MS demonstrates outstanding sensitivity and repeatability, which are due in large part to unique design features of the ion optics.

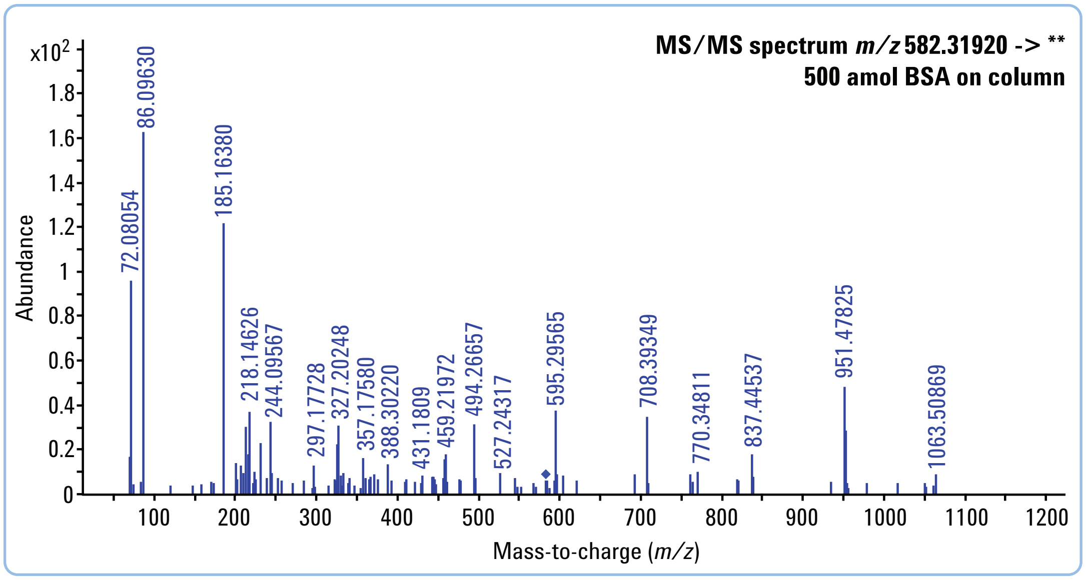

Figure 17. Analysis of 500 amol of BSA injected on column demonstrates the superb sensitivity of the 6510 Quadrupole Time-of-Flight LC/MS. Protein database searching on this data provided positive identification.

References

1. John Fjeldsted, "Time-of-Flight Mass Spectrometry," *Agilent Technical Overview, Publication Number 5989-0373EN,* **2003**.

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