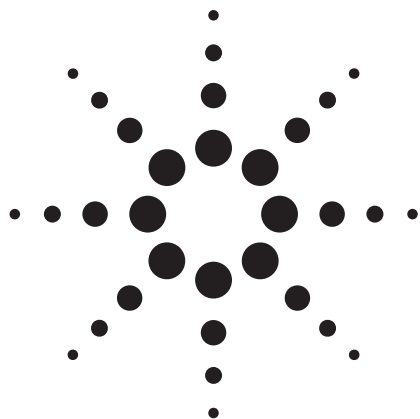




Time-of-Flight Mass Spectrometry

Technical Overview

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Introduction

Time-of-flight mass spectrometry (TOF MS) was developed in the late 1940's, but until the 1990's its popularity was limited. Recent improvements in TOF technology, including orthogonal acceleration, ion mirrors (reflectrons), and high-speed electronics, have significantly improved TOF resolution. This improved resolution, combined with powerful and easy-to-use electrospray (ESI) and matrix-assisted laser desorption ionization (MALDI) ion sources, have made TOF MS a core technology for the analysis of both small and large molecules.

This overview describes:

- Basic theory of operation for an orthogonal acceleration time-of-flight (oa-TOF) mass spectrometer
- Flight time and the fundamental equations for TOF mass analysis
- TOF measurement cycle
- Relative advantages of the two most common TOF digitizers — analog-to-digital converter (ADC) and time-to-digital converter (TDC)
- Theoretical and practical limits to mass accuracy
- Dynamic range considerations

Basic oa-TOF MS Theory of Operation

While an orthogonal acceleration time-of-flight mass spectrometer can be interfaced with many types of ion sources, this discussion will focus on the use of an oa-TOF MS with atmospheric pressure ionization (API) sources. There are several types of API sources that can be used, including:

- Electrospray ionization (ESI) at various flow rates
- Atmospheric pressure chemical ionization (APCI)
- Atmospheric pressure photoionization (APPI)
- Atmospheric pressure matrix-assisted laser desorption ionization (AP-MALDI)



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Ions from these sources can be introduced into the mass spectrometer vacuum system via a common atmospheric sampling interface.

Figure 1 depicts the Agilent LC/MSD TOF, an oa-TOF mass spectrometer. Ions produced in the source are electrostatically drawn through heated drying gas and then through a sampling capillary into the first stage of the vacuum system. Near the exit of the capillary is a metal skimmer with a small hole. Heavier ions with greater momentum pass through the skimmer aperture. Most of the lighter drying gas (nitrogen) molecules are pumped away by a vacuum pump.

The ions that pass through the skimmer and enter the second stage of the vacuum system are immediately focused by the first of two octopole ion guides. An octopole ion guide is a set of small parallel metal rods with a common open axis through which the ions can pass. Radio frequency (RF)

voltage applied to the rods creates electromagnetic fields that confine ions above a particular mass to the open center of the rod set. The ions are propelled through this first octopole ion guide by the momentum retained from being drawn from atmospheric pressure through the sampling capillary. As the ions transit the first octopole, they also pass into the third stage of the vacuum system, where the pressure is now low enough that there are few collisions between the ions and gas molecules.

Ions exiting the first octopole ion guide immediately enter the second octopole ion guide in the fourth vacuum stage. The second octopole ion guide is similar to the first, but carries a lower direct current (DC) potential. It accelerates the ions. The second ion guide is driven by an RF power amplifier operated at 5 MHz. The high 5 MHz frequency is key to achieving maximum ion transmission over a wide ($> m/z$ 100– m/z 3000) mass range.

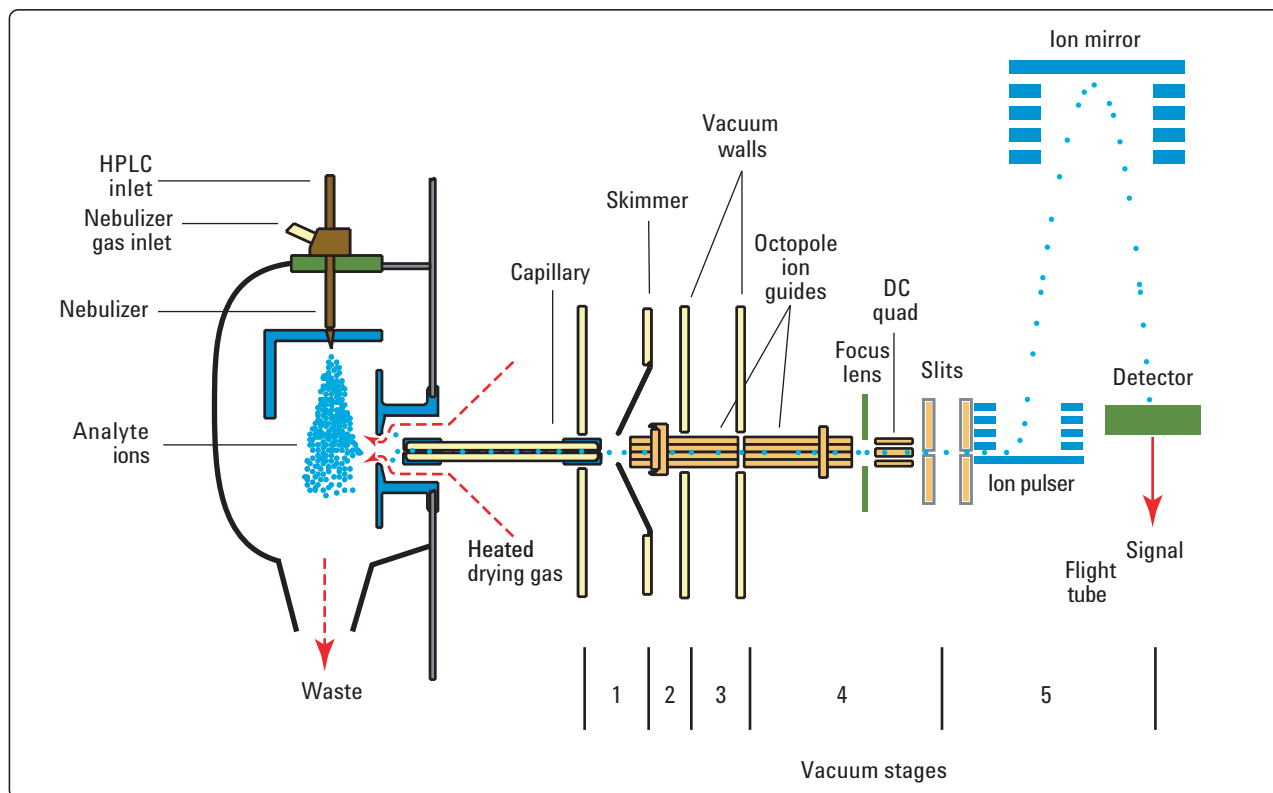


Figure 1. Ion source, ion optics, and mass filter from the Agilent LC/MSD TOF, an API oa-TOF mass spectrometer

In the fourth vacuum stage, the ion beam leaves the second octopole ion guide and enters the beam-shaping optics. An ion focus lens and DC quadrupole shape the beam to achieve optimal parallelism and size before it enters the time-of-flight mass analyzer. The more parallel the ion beam, the higher the resolving power that can be achieved.

After the ions have been shaped into a parallel beam, they pass through a pair of slits into the fifth and last vacuum stage, where the time-of-flight mass analysis takes place. Because the mass of each ion is assigned based on its flight time, the background gas pressure in this stage must be very low. Any collision of an ion with residual background molecules will alter the flight time of the ion and affect the accuracy of its mass assignment.

In the time-of-flight mass analyzer, the nearly parallel beam of ions first passes into the ion pulser. The pulser is a stack of plates, each (except the back plate) with a center hole. The ions pass into this stack from the side just between the back plate and the first plate.

To start the ion's flight to the detector, a high-voltage (HV) pulse is applied to the back plate. This accelerates the ions through the stack of pulser plates.

The ions leave the ion pulser and travel through the flight tube, which is about one meter in length. At the opposite end of the flight tube is a two-stage, electrostatic ion "mirror" that reverses the direction of the ions back towards the ion pulser. The two-stage mirror has two distinct potential gradients, one in the beginning section and one deeper in the mirror. This improves second-order time focusing of the ions on the detector. Because ions enter the ion pulser with a certain amount of horizontal momentum, they continue to move horizontally as well as vertically during their flight. Thus, they are not reflected directly back to the ion pulser, but instead arrive at the detector.

Figure 2 shows a schematic of the detector. The first stage of the detector is a microchannel plate (MCP), a thin plate perforated by many precise microscopic tubes (channels). When an ion with sufficient energy hits the MCP, one or more elec-

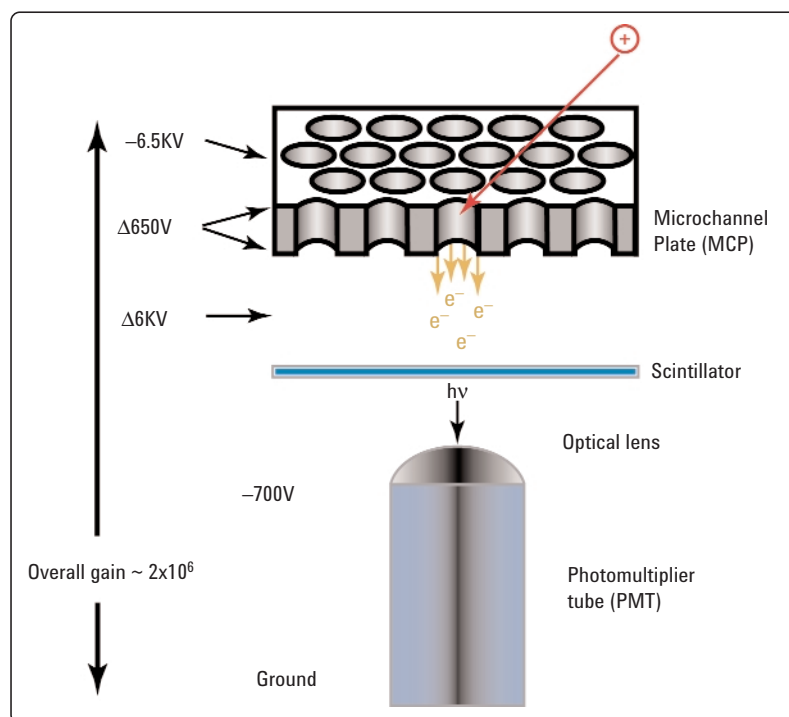


Figure 2. TOF detector with potentials shown for positive ion operation

trons are freed. Each microchannel acts as an electron multiplier. By the time the electrons exit the MCP, there are roughly ten electrons for every incoming ion.

The electrons exiting the MCP are accelerated onto a scintillator that, when struck by the electrons, emits photons. The photons from the scintillator are focused through optical lenses onto a photomultiplier tube (PMT), which amplifies the number of photons and then produces a electrical signal proportional to the number of photons.

The reason for this conversion of an electrical signal to an optical signal and back to an electrical signal is to electrically isolate the flight tube and the front of the detector, which are at roughly -6,500 volts, from the PMT, whose signal output is at ground potential.

Flight Time and Its Relationship to Mass

Equations for time-of-flight

The flight time for each mass is unique. It starts when a high voltage pulse is applied to the back plate of the ion pulser and ends when the ion strikes the detector. The flight time (t) is determined by the energy (E) to which an ion is accel-

erated, the distance (d) it has to travel, and its mass (strictly speaking its mass-to-charge ratio). There are two well know formulae that apply to time-of-flight analysis. One is the formula for kinetic energy:

$$E = \frac{1}{2}mv^2$$

which solved for m looks like:

$$m = 2E/v^2$$

and solved for v looks like:

$$v = \sqrt{(2E/m)}$$

The equation says that for a given kinetic energy, E , smaller masses will have larger velocities, and larger masses will have smaller velocities. That is exactly what takes place in the time-of-flight mass spectrometer. Ions with lower masses arrive at the detector earlier, as shown in Figure 3. Instead of measuring velocity, it is much easier to measure the time it takes an ion to reach the detector.

The second equation is the familiar velocity (v) equals distance (d) divide by time (t):

$$v = d/t$$

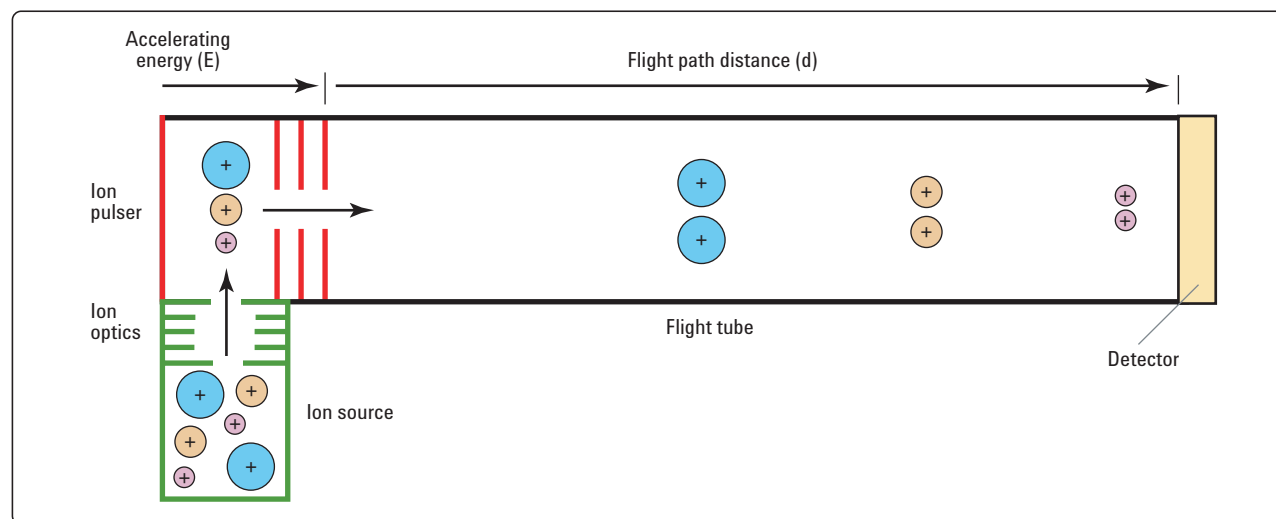


Figure 3. Time-of-flight analysis of ions of various masses, each with a single charge. For clarity and simplicity, this shown in a linear time-of-flight mass spectrometer that does not have an ion mirror.

Combining the first and second equations yields:

$$m = (2E/d^2)t^2$$

This gives us the basic time-of-flight relationship. For a given energy (E) and distance (d), the mass is proportional to the square of the flight time of the ion.

In the design of an oa-TOF mass spectrometer, much effort is devoted to holding the values of the energy (E) applied to the ions and the distance (d) the ion travels constant, so that an accurate measurement of flight time will give an accurate mass value. As these terms are held constant they are often combined into a single variable, A, so:

$$m = At^2$$

This is the ideal equation that determines the relationship between the flight time of an ion and its mass. Because the relationship is a squared relationship, if the observed flight time of the ion is doubled, the resulting mass is not doubled, but rather it is four times greater.

In practice, there is a delay from the time the control electronics send a start pulse to the time that high voltage is present on the rear ion pulser plate. There is also a delay from the time an ion reaches the front surface of the ion detector until the signal generated by that ion is digitized by the acquisition electronics. These delays are very short, but significant. Because the true flight time cannot be measured, it is necessary to correct the measured time, t_m , by subtracting the sum of both the start and stop delay times which, when added together, are referred to as t_0 .

$$t = t_m - t_0$$

By substitution, the basic formula that can be applied for actual measurements becomes:

$$m = A(t_m - t_0)^2$$

Mass calibration

To make the conversion from measured flight time, t_m , to mass, the values of A and t_0 must be

determined, so a calibration is performed. A solution of compounds whose masses are known with great accuracy is analyzed. Then, a simple table is established of the flight times and corresponding known masses. It looks something like this:

Table 1. TOF mass calibration

Calibrant compound mass (u)	Flight time (μ sec)
118.0863	20.79841
322.0481	33.53829
622.029	46.12659
922.0098	55.88826
1521.971	71.45158
2121.933	84.14302
2721.895	95.13425

Now that m and t_m are known for a number of values across the mass range, the computer that is receiving data from the instrument does the calculations to determine A and t_0 . It employs nonlinear regression to find the values of A and t_0 so that the right side of the calibration equation,

$$m = A(t_m - t_0)^2$$

matches as closely as possible the left side of the equation (m), for all seven of the mass values in the calibration mix.

While this initial determination of A and t_0 is highly accurate, it is not accurate enough to give the best possible mass accuracy for time-of-flight analysis. A second calibration step is needed. So after the calibration coefficients A and t_0 have been determined, a comparison is made between the actual mass values for the calibration masses and their calculated values from the equation. These typically deviate by only a few parts-per-million (ppm). Because these deviations are small and relatively constant over time, it is possible to perform a second-pass correction to achieve an even better mass calibration. This is done with an equation that corrects the small deviations across the entire mass range. This correction equation, a higher-order polynomial function, is stored as

part of the instrument calibration. The remaining mass error after this two-step calibration method, neglecting all other instrumental factors, is typically at or below 1 ppm over the range of calibration masses.

Reference mass correction

Achieving an accurate mass calibration is the first step in producing accurate mass measurements. When the goal is to achieve mass accuracies at or below the 3 ppm level, even the most miniscule changes in energy applied to the ions can cause a noticeable mass shift. It is possible, however, to cancel out these factors with the use of reference mass correction. With this technique, one or more compounds of known mass are introduced into the ion source at the same time as the samples. The instrument software constantly corrects the measured masses of the unknowns using the known masses as reference.

Reference mass correction is a technique that has been automated on the Agilent LC/MSD TOF mass spectrometer. To introduce reference compounds, a second nebulizer has been integrated into the ESI ion source. This reference nebulizer is connected to the 'A' bottle of the calibrant delivery system (CDS), which is controlled via software. Bottle A contains the reference compounds.

The mass spectrometer control software has an editable table that contains the exact masses of these reference compound ions. During the acquisition of each spectrum from the time-of-flight analyzer, these known masses are identified and the A and t_0 values are re-optimized. Each stored spectrum has its own A and t_0 values so that the software can adjust for even the smallest instrument variation. Each spectrum is then corrected using these values and using the correction equation (the higher-order polynomial function) determined in the second calibration step described previously. The correction equation needs to be determined only once because the small deviations across the mass range are nearly constant over time.

To determine the two unknowns, A and t_0 , the reference compounds must contain at least two

components of known mass. In order to achieve a good fit for both A and t_0 , at least one reference mass needs to be a low mass value and at least one needs to be a higher mass value. For best results, the low m/z and high m/z reference masses should bracket the masses of analytical interest. The reference mass correction algorithm for the LC/MSD TOF requires that one mass be at or below m/z 330 and that a second mass be at least 500 m/z above the low mass ion. If these conditions are not satisfied, but at least one reference mass is found, then only the A term is recalculated.

TOF Measurement Cycle

TOF measurements do not rely on the arrival times of ions coming from just a single pulse applied to the ion pulser, but instead are summations of the signals resulting from many pulses. Each time a high voltage is applied to the plates of the ion pulser, a new spectrum called a single transient is recorded by the data acquisition system. This is added to previous transients until a predetermined number of sums has been made. For analyses requiring a scan speed of one spectrum per second, approximately 10,000 transients can be summed before transferring the data from the instrument back to the host computer to be written to disk. If the target application involves high speed chromatography, then fewer transients are summed, increasing the scan speed.

The mass range limits the number of times per second that the ion pulser can be triggered and transients recorded. Once the ion pulser fires, it is necessary to wait until the last mass of interest arrives at the ion detector before the ion pulser is triggered again. Otherwise light ions triggered from the second transient could arrive before the heavier ions of the first transient, resulting in overlapping spectra.

Table 2 shows some example masses with their approximate flight times and possible transient rates. These are calculated for a flight length of two meters and a flight potential of 6,500 volts. Under these conditions, a ion with m/z 3200 has a flight time of about 0.1 milliseconds (msec), or 100 microseconds (μ sec). Because there is essen-

tially no delay time between transients, this means that 10,000 transients per second correspond to a mass range of 3200 m/z . For a smaller mass range, the ion pulser can be triggered at higher rates. For example, a mass of m/z 800 (one-fourth of 3200 m/z) reduces the flight time to 0.1 msec/ $\sqrt{4}$, or 0.05 milliseconds, allowing for 20,000 transients per second over an 800 m/z mass range. Conversely, extending the transient to 0.141 milliseconds doubles the mass range to 6400 m/z (mass is a function of the time squared).

Table 2. Flight time and transients/second as a function of mass*

m/z	Flight time (μ sec)	Transients/sec
800	50	20,000
3200	100	10,000
6400	141	7,070

*Two-meter flight tube, flight potential 6500V. The minimum allowed transient is 50 μ sec (50,000 points). The maximum is 160 μ sec (160,000 points) or about 8,000 m/z .

Because transients are so short, the number of ions of a specific mass from a particular compound in any given transient is generally quite small. For many oa-TOF instruments, this number averages to substantially less than one. This fact plays an important role in the basic design of the data acquisition system of many of today's commercial instruments.

Digitally Recording Ion Arrival

While there is an exact instant when each ion strikes the detector, it is difficult to transfer this perfectly into the digital world. There are two basic approaches used to translate a detector signal into a digital measurement: the analog-to-digital converter (ADC) used in the Agilent LC/MSD TOF and the time-to-digital converter used in many other commercial TOF systems. The next two sections discuss these two approaches.

Analog-to-digital converter systems

The function of an analog-to-digital converter (ADC) is to represent digitally the signal that comes from the ion detector. An ADC does not attempt to determine the exact arrival time of the ions; it is simply a data recorder. As a data recorder, it samples the amplified detector output at a fixed interval. In the case of the LC/MSD TOF, this interval is 1 nanosecond (10^{-9} seconds). This translates to a frequency of one gigahertz (GHz), or 1 billion cycles per second. During each cycle the detector output signal intensity is converted into a digital value. The digital value is represented by eight bits, corresponding to a dynamic range of 2^8 counts, or in decimal notation 0 to 255 counts.

When the acquisition system signals the pulser to fire, the ADC begins to convert the signal arriving from the detector amplifier. It stores each successive conversion in memory. Each time the pulser fires, the ADC adds the new measurement to those already recorded in memory from the previous transients. When an ADC is used in this way, it is called an integrating transient recorder.

With an ADC, some care must be used to bias the detector amplifier (Amp Offset) to a value close to zero so that when no ion signal is present, zero signal is recorded. Otherwise, the signal present in the absence of an ion signal would add to system noise. The gain of the detector and amplifier must be sufficient so that an individual ion registers at least one count. In practice, the gain is normally set so that the average number of counts per ion is greater than one. The LC/MSD TOF autotune routine automatically sets the detector gain and Amp Offset parameters to satisfy these conditions.

The advantage of the ADC acquisition system relative to the TDC acquisition system (discussed in the next section) becomes apparent when multiple ions of a given mass arrive at the detector within a single transient. The detector is an analog device and amplifies the combined signal from the several nearly simultaneous ion arrivals. An ADC with its eight bits can translate this rising and falling signal into a digital profile of the mass peak, as

shown in Figure 4. Each successive transient builds the values in memory. This accurately represents the detector output signal, whether it is from a small or large ion current. The next section will show why the TDC does not have this dynamic range.

Time-to-digital converter systems

The time-to-digital converter (TDC) represents the second approach to digitizing a TOF signal. A TDC acquisition system begins with a discriminator. A discriminator is an electronic device that triggers when a particular signal level is reached. This trigger signal from the discriminator is registered by a counter, which marks the flight time. After a brief dead time, the discriminator and counter are ready to record the next ion arrival.

Since the discriminator triggers on the leading edge of the mass peak, the advantage of a TDC system is its ability to eliminate any broadening of the mass peak originating in the detector and amplifier. One disadvantage is loss of dynamic range. Since the discriminator triggers on the leading edge of the incoming ion signal, it ignores the remainder of the detector signal and gives the same response regardless of whether the signal is the result of one ion or many ions. The TDC simply marks ion arrival, but cannot convey how

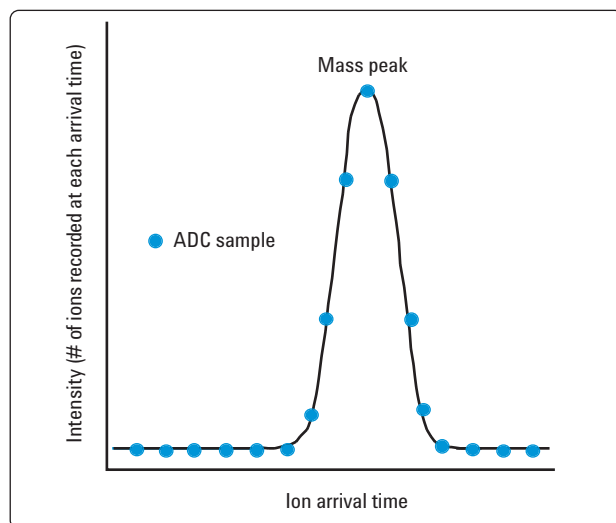


Figure 4. An ADC can record multiple ions per transient, so it accurately tracks ion signal intensity

many ions. Because the repetition rate for transients is high, and the average number of ions for any given mass has been substantially less than one per transient, this has generally been an “acceptable” solution. However, as ion sources and ion optics become more efficient, the number of ions of a given mass in a single transient increases to the point of significance.

To illustrate this, consider a hypothetical instrument equivalent to the LC/MSD TOF that uses a TDC acquisition system. Figure 5 shows the number of ions for a single compound that arrive in a single transient, as a function of sample amount. At sample concentrations above 1000 picograms, the hypothetical TDC system no longer gives an increased signal response because the TDC cannot reflect the fact that multiple ions of a given mass are arriving in each transient.

A second problem associated with TDC acquisition systems is an observed shift in measured ion arrival time at high ion currents. When less than one ion for any given mass arrives at the detector per transient, the TDC accurately records arrival time to within the limit of the counter’s resolution. If ions arrive for a given mass just slightly separated in time (as determined by the instrument’s

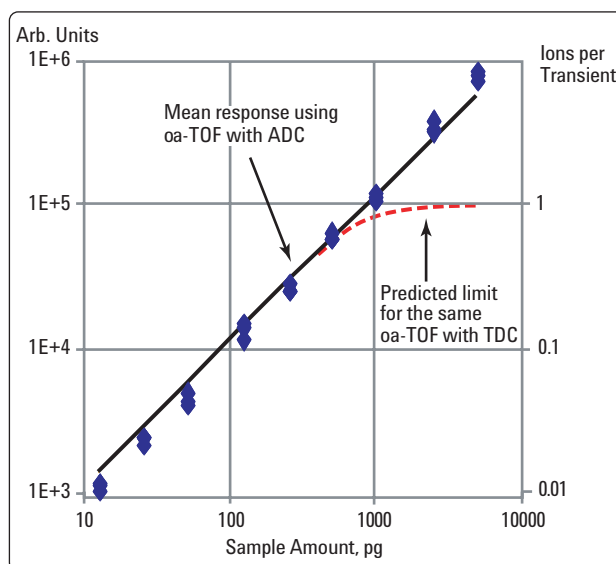


Figure 5. Ions per transient as a function of sample amount, showing TDC limitations

resolving power) then, unless the signal from the detector has returned to below the threshold point, the second ion is unable to trigger the discriminator (see Figure 6). This phenomenon and the associated reset time of the discriminator and counter are called TDC dead time.

TDC dead time can have a significant effect in attempts to accurately measure average ion arrival times. If a significant number of ions arrive at the detector during the TDC dead time, then a shift in the average of the arrival distribution occurs. The shift in the measured ion arrival time is always to shorter arrival times, because it is always the second ion to arrive in a given transient that is dropped. The shift towards shorter apparent arrival time directly translates to a smaller mass value. When attempting to measure mass values to the part-per-million accuracy, even a few ions missed can have a substantial effect.

The discriminator used on TDC systems also introduces a third problem. The arrival of each ion produces a peak with measurable width. With an ADC system, the peak is profiled with multiple points within a single transient. These points can be subjected to mathematical centroiding to calculate the arrival time with high accuracy. Centroiding allows calculation of the ion arrival time to a resolution beyond that given by the original data points. With a TDC system, the arrival of the ion is captured by a single value. This means the time between data acquisitions must be shorter to achieve the same time resolution. Because of the loss of the arrival profile information, TDC systems must operate at higher sampling rates to achieve equivalent mass accuracy even when saturation effects are not present.

Theoretical and Practical Limits to Mass Accuracy

Whether the acquisition system is a TDC or an ADC, the arrival time for the accumulated signal in memory is determined by centroiding the mass measurements from the individual transients. Even though the focus of the design of the TDC was to specifically measure the arrival time of

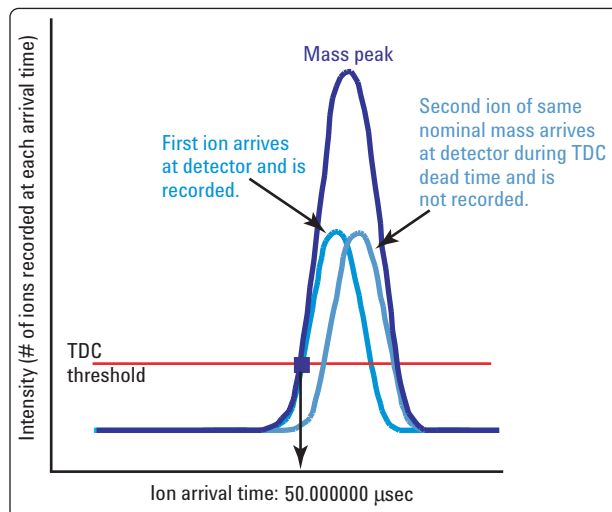


Figure 6. TDC dead time causes shift to shorter arrival times for higher signal levels

each ion, the nominal arrival time must be the average (centroid) of the population for the summed transients. There are limits to how precisely this centroid can be determined.

Ion statistics

The first theoretical limit is set by the number of ions measured and their time distribution. If the distribution is narrow and well populated, resulting in a quiet and stable signal, then the centroid or average can be precisely determined. The expression is:

$$\sigma = 10^6 / (2.4 * R * \sqrt{n})$$

where σ is the standard deviation of the resulting measurement, R is the resolving power (often called resolution) of the mass spectrometer and n is the number of ions that are detected in the mass peak. Suppose one desires 95% confidence 2σ mass accuracy at 3 ppm. Then with a resolving power of 10,000 (and $1\sigma = 1.5$ ppm) it is necessary to have approximately 1000 ions. To increase the number of ions in a centroided spectrum, it is general practice to use the data analysis software to average spectra across the width of the eluting chromatographic peak.

It should be noted that while oa-TOF has the potential for fast scan cycles, reducing the scan time reduces the number of transients, which reduces the integration of ions required to achieve accurate mass measurements. Fast scanning and accurate mass are opposing performance goals. The most accurate mass measurements are achieved under slower scanning conditions.

Chemical background

The second significant factor that limits mass accuracy is chemical background. The high resolving power of a TOF system helps to reduce the chances of having the peak of interest merged with background, yet even a small unresolved impurity can shift the centroid of the expected mass. The magnitude of this effect can be estimated by using a simple weighted average calculation.

$$\Delta_{\text{obs}} = \frac{\Delta_{\text{contaminant}}^{1/2} \text{Abd}_{\text{contaminant}}}{(\text{Abd}_{\text{contaminant}} + \text{Abd}_{\text{sample}})}$$

where

Δ_{obs} is the observed shift in mass in ppm

$\Delta_{\text{contaminant}}$ is the mass difference between the sample and contaminant in ppm

$\text{Abd}_{\text{contaminant}}$ and $\text{Abd}_{\text{sample}}$ are the mass peak heights or areas of the contaminant and sample

By way of example, for a resolving power of 10,000, a mass difference between the sample and contaminant of 50 ppm, and relative mass peak heights of 10:1 (sample vs background) the observed mass shift would be $50 \times 1/(1 + 10)$ or about 5 ppm.

There are a number of ways to minimize chemical background. First, the Agilent LC/MSD TOF has a sealed ion source design that minimizes contamination from the laboratory air. Second, very high purity HPLC solvents should always be used. Third, a regular, systematic cleaning program for the HPLC and the MS ion source should be followed. These precautions help ensure the highest quality mass measurements.

Dynamic Range

Dynamic range can be measured in various ways. Probably the most exacting definition for mass spectrometry is the “in-scan” condition. This is the dynamic range within a single spectrum, defined as the ratio in signal abundance of the largest and smallest useful mass peaks.

Even when restricted to the in-scan definition of dynamic range, the upper and lower limits must be defined. There are both theoretical and practical limits to consider. Theoretically, it is possible to detect a single ion, but practically, chemical background would, under most conditions, obscure such a low level. Practical limitations depend on the application. For example, when the instrument is used for accurate mass measurement, then the lower limit is set by the minimum sample amount for which accurate mass measurements can be obtained.

To determine the minimum sample amount, the limitations based on ion statistics must be considered. Assuming a goal of 5 ppm mass accuracy, achieved with 67% confidence (1σ) based on a single unaveraged spectrum and allowing for 1 ppm of calibration error, then $1\sigma = 4$ ppm. Staying with the assumption of 10,000 resolving power, then about 200 ions are required for the measurement. This calculation is based on ion statistics and resolving power, and is independent of acquisition technology. This calculation does assume that there is significant sensitivity (signal-to-noise) so that the measurement is unaffected by background contamination.

To determine the highest level under which accurate mass measurements can be obtained, the type of acquisition system must be considered. With a TDC system, there is a theoretical limit at one ion per transient at a given mass. With an ADC system, depending on the detector gain, many ions can be accurately measured for a given mass in a single transient. The LC/MSD TOF auto-tune software targets the detector gain for a mean ion response of five counts. In a single transient, the ADC with 8 bits or 255 counts can therefore measure up to 50 ions for a given mass.

Practical considerations limit both TDC and ADC systems with regards to the upper limit for which accurate mass measurements can be achieved. For a TDC system, long before the level of one ion for a given mass per transient is reached, substantial mass shifts are observed. Deadtime correction algorithms compensate for this, but these corrections are effective only up to some fraction of this theoretical limit, typically 0.2 to 0.5 ions/transient. Both ADC and TDC systems, when used to make measurements on rising and falling chromatographic peaks, need to allow for a safety buffer of a factor of two. This is because the chromatographic peak may be rising into saturation, even while the average of the 10,000 transients used to make the final mass measurement is at only the 50% level.

Table 3 summarizes both theoretical and practical dynamic range limits for ADC- and TDC-based oa-TOF mass spectrometers, based on single-spectrum, in-scan dynamic range.

Depending on the application, it is sometimes possible to extend the practical dynamic range. One approach is to sum (average) multiple spectra together. This improves ion statistics and allows for increased mass accuracy at lower sample levels.

To extend the dynamic range on the high end, the opposite approach is taken and spectra from the apex of a chromatographic peak are excluded from the average. Intelligent spectral averaging is an important function of the automated accurate mass report generation software of the LC/MSD TOF. Together these techniques can extend the practical limit of dynamic range ($\sim 10^3$) by a factor of 100, achieving effective dynamic ranges of 10^5 for ADC-based systems in accurate mass applications.

Conclusion

Over the past few years, there has been substantial progress in technologies that take the oa-TOF to new performance levels. High-efficiency ion optics and vacuum system designs have given rise to greater sensitivities. High-speed ADC-based acquisition systems have made greater mass accuracy and wider dynamic range possible. The addition of sophisticated data systems and data processing algorithms has enabled outstanding mass accuracies under routine analysis conditions. By understanding the concepts of oa-TOF mass spectrometry, it is possible to achieve the ultimate in performance with the Agilent LC/MSD TOF system.

Table 3. Single spectrum in-scan dynamic range

	LC/MSD TOF	Hypothetical TDC System
Theoretical Limit		
Minimum detectable per spectrum (ions/spectrum)	1	1
Maximum detectable per transient (ions/transient)	50	1
Maximum detectable per spectrum ($\times 10,000$ transients)	500,000	10,000
Dynamic range	500,000	10,000
Practical Limit (while achieving accurate mass)		
Lower limit per spectrum (ions/spectrum)	200	200
Upper limit per transient (ions/transient)	25	0.1–0.25
Upper limit per spectrum ($\times 10,000$ transients)	250,000	1000–2500
Dynamic range	1,250	10–25

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