TECHNICAL NOTE

ICP-Mass Spectrometry

The 30-Minute Guide to ICP-MS

A Worthy Member of the Inorganic Analysis Team

For nearly 30 years, inductively coupled plasma–mass spectrometry (ICP-MS) has been gaining favor with laboratories around the world as the instrument of choice for performing trace metal analysis. While atomic absorption (AA) and inductively coupled plasma-optical emission (ICP-OES) systems dominate the inorganic analysis landscape, ICP-MS continues to make inroads into laboratories that are requiring the lowest detection limits and the greatest level of productivity. According to recent data provided by the Joint ALSSA-JAIMA-Eurom II Global Laboratory Analytical Instruments Booking Report, over 15% of all new instruments purchased for trace metal analysis are ICP-MS instruments.

The primary reasons for the growing popularity of ICP-MS can be summarized in a few points:

- Instrument detection limits are at or below the single part per trillion (ppt) level for much of the periodic table
- Analytical working range is nine orders of magnitude
- Productivity is unsurpassed by any other technique
- Isotopic analysis can be achieved readily

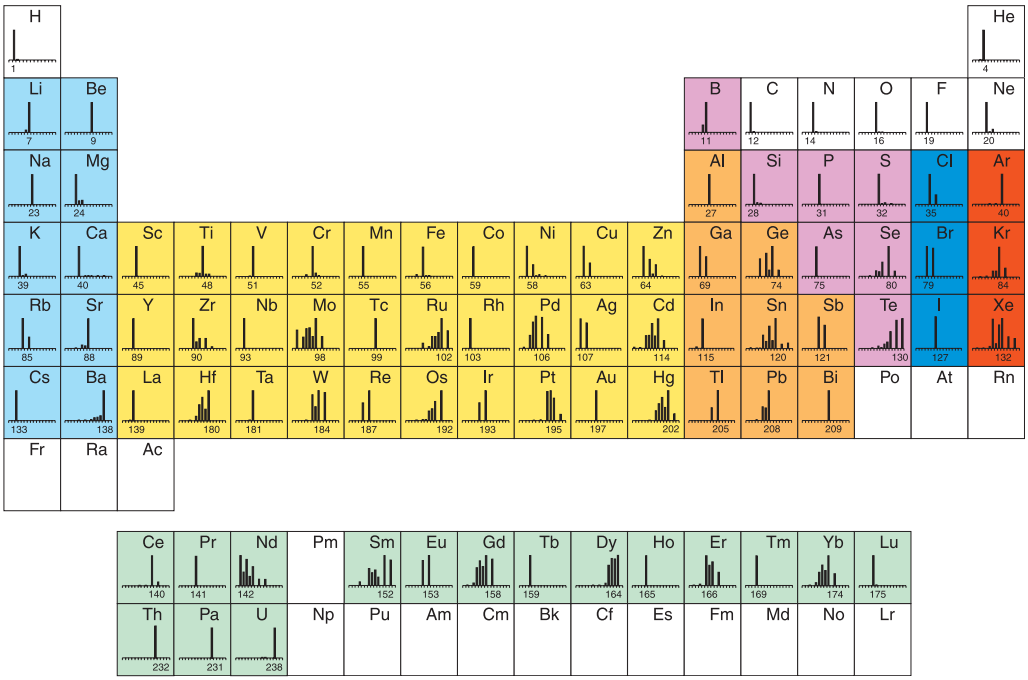

Figure 1. Elements analyzed by ICP-MS (in color).

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For the Better

What can be measured with an ICP-MS?

The ICP-MS instrument measures most of the elements in the periodic table. The elements shown in color in Figure 1 can be analyzed by ICP-MS with detection limits[a] at or below the ppt[b] range. Elements that are in white are either not measurable by ICP-MS (the upper right-hand side) or do not have naturally occurring isotopes.

Most analyses performed on ICP-MS instrumentation are quantitative; however, it also can serve as an excellent semi-quantitative instrument. By using a semi-quantitative software package, an unknown sample can be analyzed for 80 elements in three minutes, providing semi-quantitative data that is typically within ±30% of the quantitative values.

For reasons that often involve human health, knowing the isotopic composition of a sample can be highly important. Of the three techniques mentioned to this point, only ICP-MS is used routinely for determining isotopic composition.

How does ICP-MS work?

Before getting into the individual components of an ICP-MS instrument, let's take a minute to understand the overall science of the technique.

Samples are introduced into an argon plasma as aerosol droplets. The plasma dries the aerosol, dissociates the molecules, and then removes an electron from the components, thereby forming singly-charged ions, which are directed into a mass filtering device known as the mass spectrometer. Most commercial ICP-MS systems employ a quadrupole mass spectrometer which rapidly scans the mass range. At any given time, only one mass-to-charge ratio will be allowed to pass through the mass spectrometer from the entrance to the exit. If, for example, the quadrupole was set to allow ions with a mass to charge ratio of 23/1 to pass through, we would find that sodium (Na) ions would, while all other singly charged ions would not.

Upon exiting the mass spectrometer, ions strike the first dynode of an electron multiplier, which serves as a detector. The impact of the ions releases a cascade of electrons, which are amplified until they become a measureable pulse. The software compares the intensities of the measured pulses to those from standards, which make up the calibration curve, to determine the concentration of the element.

For each element measured, it is typically necessary to measure just one isotope, since the ratio of the isotopes, or natural abundance, is fixed in nature. It may be helpful to refer again to Figure 1 where you will see a simple bar graph for each element. The bars depict the number and relative abundance of the natural isotopes for that element, which is sometimes referred to as the isotopic fingerprint of the element. If you noticed, earlier in this paragraph, the word "typically" was used because there is an element that does not follow the natural abundance rule: lead (Pb). Naturally occurring lead originates from two sources – some was placed here when the earth was born and some is the result of the decay of radioactive materials. This creates a situation where the lead isotope ratios may vary depending on the source of the lead. To be sure that we accurately measure the concentration of lead in a sample, it is necessary to sum several of the isotopes available.

ICP-MS can be used to measure the individual isotopes of each element; this capability brings value to laboratories interested in one specific isotope of an element or in the ratio between two isotopes of an element.

A quick overview

An ICP-MS consists of the following components:

- Sample introduction system – composed of a nebulizer and spray chamber and provides the means of getting samples into the instrument
- ICP torch and RF coil – generates the argon plasma, which serves as the ion source of the ICP-MS
- Interface – links the atmospheric pressure ICP ion source to the high vacuum mass spectrometer
- Vacuum system – provides high vacuum for ion optics, quadrupole, and detector
- Collision/reaction cell – precedes the mass spectrometer and is used to remove interferences that can degrade the detection limits achieved. It is possible to have a cell that can be used both in the collision cell and reaction cell modes, which is referred to as a universal cell
- Ion optics – guides the desired ions into the quadrupole while assuring that neutral species and photons are discarded from the ion beam
- Mass spectrometer – acts as a mass filter to sort ions by their mass-to-charge ratio *(m/z)*
- Detector – counts individual ions exiting the quadrupole
- Data handling and system controller – controls all aspects of instrument control and data handling to obtain final concentration results.

Now it is time to take a closer look at each of these components.

a The detection limits are based on a 98% confidence level (3 standard deviations).

b Identifying a single ppt of an element in a solution analogous to locating a single white raisin in a house (2700 sq. ft. or 260 square meters) full of regular raisins.

Sample introduction – making the right sized droplets

As mentioned earlier, most samples introduced into an ICP-MS system are liquids. It is necessary to break the liquid sample into small droplets before they can be introduced into the argon plasma. The liquid sample may be introduced by a peristaltic pump or through self aspiration to a nebulizer that creates an aerosol of fine droplets. The type of nebulizer used can depend upon the viscosity, cleanliness, and even the available volume of the sample to be analyzed. Some of the more commonly used nebulizers used with ICP-MS systems include:

- Concentric
- Cross-flow
- Babington

Within these three general categories of nebulizers, there exist a number of variations on the general design, so it is likely that you will encounter nebulizers identified as V-Groove, GemCone™, HEN (High Efficiency Nebulizer), MCN (Micro Concentric Nebulizer), etc. Each of these specialty nebulizers can enhance the introduction of specific sample types leading to overall improved performance of the ICP-MS.

The fine droplets created by the nebulizer will most often be passed through a spray chamber before they are allowed to enter the plasma. Most commercially provided spray chambers fall into two categories:

- Scott
- Cyclonic

Once again, we will see many variations on the theme, with spray chambers manufactured from polymers, glass, and quartz. Also, spray chambers can be baffled, cooled or contain desolvation devices to improve their action. Regardless of the design, the desired end result is to allow a substantial number of the small droplets created by the nebulizer to enter the torch while discarding the larger droplets which can create analytical issues if allowed to enter the torch.

The ICP torch – making ions

The plasma generated in the ICP torch creates a very hot zone that serves a variety of functions. At a temperature of approximately 6000 °C, the plasma is about 10 times hotter than a pizza oven, three times hotter than a welding torch, and equal to the temperature at the surface of the sun. The plasma is generated by passing argon through a series of concentric quartz tubes (the ICP torch) that are wrapped at one end by a radio frequency (RF) coil. Energy supplied to the coil by the RF generator couples with the argon to produce the plasma.

During their voyage into the plasma, the liquid droplets, containing the sample matrix and the elements to be determined, are dried to a solid and then heated to a gas. As the atoms continue their travel through the plasma, they absorb more energy and eventually release one electron to form singly charged ions. The singly charged ions exit the plasma and enter the interface region.

The interface – sampling ions

Placing a plasma, operating at 6000 °C, near an ion focusing device operating near room temperature is a bit like placing the earth about a half-mile away from the sun. In addition to a large temperature difference, the plasma operates at a pressure that is much higher than the vacuum required by the ion lens and mass spectrometer portions of the instrument.

The interface allows the plasma and the ion lens system to coexist and the ions generated by the plasma to pass into the ion lens region. The interface consists of two or three inverted funnel-like devices called cones.

Until recently, all commercially available ICP-MS systems used the two-cone design. Such a design requires downstream focusing of the beam that exits the interface region. This focusing has been achieved through the use of a single or a series of charged devices called ion lenses. The need for these ion lenses can be explained in Figure 2. As mentioned earlier, the plasma (located to the left of the sampler cone) operates at atmospheric pressure, while the filtering quadrupole (located to the right of the skimmer cone) operates at a very low pressure. With a two-cone design, there can only be a two-step reduction in the pressure between the plasma and filtering quadrupole. With a two-step pressure reduction, the ion beam undergoes substantial divergence as it exits the second cone, thus requiring additional focusing if the ion beam is to properly enter the filtering quadrupole.

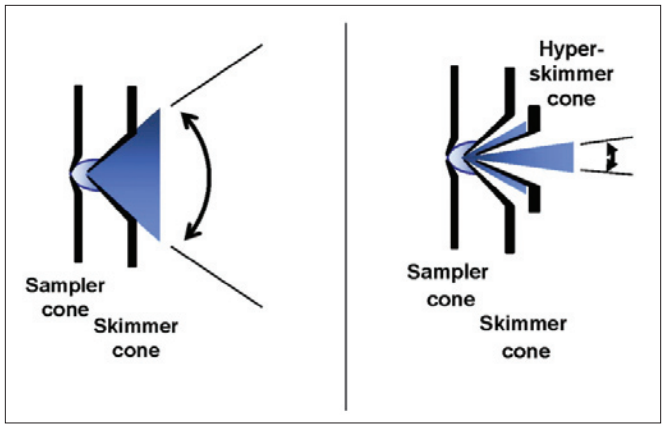

Figure 2. The two-cone design on the left shows a wide ion beam divergence resulting from a single, large pressure reduction. The three-cone design on the right shows a small ion beam divergence, resulting from two small pressure reductions.

A recent innovation has introduced a third cone into the interface which greatly reduces the divergence of the ion beam as it exits the interface region. The third cone, called the hyper-skimmer, provides a three-step reduction in pressure between the plasma and the filtering quadrupole, resulting in a substantial reduction in the divergence of the emerging ion beam. With the three-cone design, conventional ion lenses can be completely eliminated from the instrument, resulting in greater ion transmission, improved long-term stability, and reduced instrument maintenance. In the three-cone design, none of the cones has a voltage applied such as may exist on an extraction lens. Since the cones are electrically neutral, any buildup of material on their surfaces will not significantly impact their function. In addition, experience has shown that the three-cone design requires no more maintenance than a conventional two-cone design.

Cones are most often produced from nickel or platinum. While nickel cones have a lower purchase price, platinum cones provide longer life, are more resistant to some acids, and provide a small improvement in instrument performance. The orifice openings of the cones should be large enough to allow for the passage of the ion beam while, at the same time, not allow so much gas to enter the instrument that the instrument's vacuum system is taxed. Experience has shown that orifice openings of approximately 1 mm are ideal.

The vacuum system – provides correct operating pressure

The distance from the interface to the detector of an ICP-MS is typically 1 meter or less. If an ion is to travel that distance, it cannot collide with any gas molecules. This requires removal of nearly all of the gas molecules in the space between the interface and the detector.

This task is accomplished using a combination of a turbomolecular pump and mechanical roughing pump, which comprise the main components of the vacuum system. The turbomolecular pump works like a jet turbine and is capable of rapidly pumping a chamber to a pressure of 1 x 10^{-5} Torr, or less. The roughing (mechanical) pump backs the turbomolecular pump and evacuates the interface region.

Historically, maintenance of the vacuum system consisted of changing the oil in the roughing pumps every 2 to 3 months. Roughing pumps provided with fluoropolymer lubrication, such as Fomblin®, require oil changes at yearly intervals, which reduces maintenance and downtime of the instrument.

Ion deflection device – separating ions from neutrals and photons

The ion beam exiting the interface region of the instrument contains some non-ionized materials – neutrals – and photons. It is necessary that the analyte ions be separated from the neutrals and photons if high performance is to be achieved. Neutrals can collect on sensitive components of the instrument creating drift. Photons that reach the detector can be erroneously counted as ions, which increases background and degrades detection limits.

Ideally, the device used to separate the analyte ions from the neutrals and photons should be mechanically simple, stable over a long period of time, and require little or no maintenance. A quadrupole is typically used as a mass-filtering device, where the ions travel in a path parallel to the rods. It has been discovered that great utility can be gained if the ion beam is allowed to pass at a right angle (perpendicular) to the rods. When a quadrupole is placed at a right angle to the ion beam and immediately between the interface region and the filtering quadrupole, ions can be efficiently transmitted, while neutrals and photons are readily removed from the ion beam. It should be noted that the ion beam emerging from the three-cone interface is so well focused that neither the neutrals nor the photons contact any of the surfaces of the right-angled quadrupole, which effectively removes any need to clean this quadrupole. As is shown in Figure 3, the ions are turned by the quadrupole at a right angle for their entry into the filtering quadrupole or universal cell.

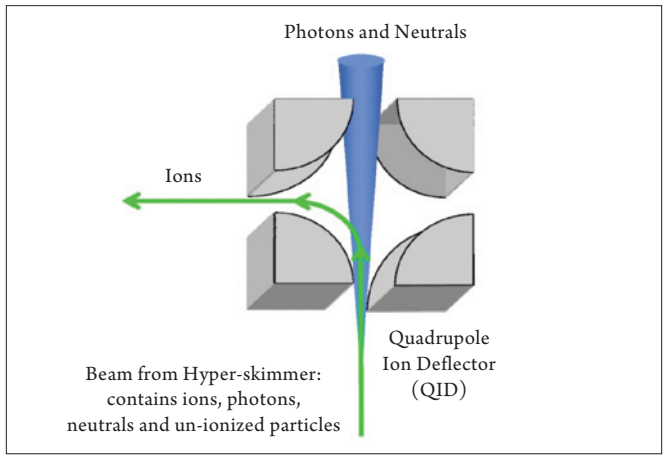

Figure 3. Diagram of a quadrupole ion deflector (QID).

The collision/reaction cell – aka "the universal cell" – keeps it clean

Interferences in ICP-MS are caused when ions generated from the plasma, the sample, or a combination of the two carry a mass-to-charge ratio that is identical to that of the analyte ion. Some common interferences and the ions impacted are shown in Table 1. Let's select one of these interferences as an example to demonstrate how collision and reaction cells function.

Argon from the plasma and oxygen from the sample matrix combine to form a polyatomic species that carries a mass of 56 amu ArO^+. Iron has several isotopes, but the isotope with the greatest abundance occurs at mass 56 also. While we may elect to use an alternative mass for iron, such as the isotope at mass 54, we will not be achieving the best detection limits possible with that isotope. If we attempt a measurement at mass 56 without removing the ArO^+ interference, we will not obtain the best possible detection limit since it will have an exceptionally high background. This is where the universal cell comes into play. The universal cell, containing the capability of operating in both collision cell and reaction cell modes, is placed between the ion optic(s) and the analyzer quadrupole.

Table 1. **Common ICP-MS interferences.**

Polyatomic Species	Interfered Analyte
$^{12}C^{15}N$, $^{12}C^{14}NH$	^{27}Al
$^{38}Ar^{1}H$	^{39}K
^{40}Ar	^{40}Ca
$^{35}Cl^{16}O$	^{51}V
$^{35}Cl^{16}O^{1}H$	^{52}Cr
$^{36}Ar^{16}O$	^{52}Cr
$^{40}Ar^{12}C$	^{52}Cr
$^{38}Ar^{16}O^{1}H$	^{55}Mn
$^{40}Ar^{16}O$	^{56}Fe
$^{40}Ar^{16}O^{1}H$	^{57}Fe
$^{40}Ar^{35}Cl$	^{75}As
ArAr	^{80}Se

When operating in the collision cell mode, the universal cell works on the straight-forward principal that the interfering ion – ArO^+ in this case – is physically larger than the analyte ion – Fe^+. If both ions are allowed to pass through a cloud of inert gas molecules, the interferent ion will collide more frequently with the inert gas atoms than will the analyte ion, due to its larger size. Each of these collisions removes a certain amount of the kinetic energy possessed by the ion. It follows then, that at the end of the ion's journey through this cloud of inert gas molecules, the analyte ion will retain more of its energy when compared to the interferent ion. An energy barrier is placed at the exit of the cell, can be adjusted so that the higher-energy analyte ions are allowed to pass through it, while the lower-energy interferences are not. This process is commonly referred to as Kinetic Energy Discrimination or KED. The collision cell will often reduce the background, but the analyte signal will also be reduced with this technique. The strength of the collision cell is the ease of method development. For samples which have great variation, such as environmental samples, one gas and one set of cell parameters will often provide an acceptable reduction in interferences.

When the universal cell is operating in the reaction cell mode, a different principal is used. Reaction cells use chemistry and take advantage of exothermic (fast) and endothermic (slow) reactions. Interferent ions tend to react with an active gas, (like ammonia), exothermally, while analyte ions react endothermally. If we pass interferent ions and analyte ions through a cloud of a reactive gas, we will find that the interferent ions will be chemically converted to a new species. In our example where ArO^+ is our interferent, the interferent ion is converted to a neutral atom. Since the neutral atom no longer carries a charge, it is not stable in the reaction cell quadrupole, and it is rapidly ejected from the cell. The analyte ion is unaffected and passes through the reaction cell and into the filtering quadrupole. The strength of the reaction cell is that it most effectively removes interferences, while almost fully preserving the analyte ions.

Not all cell-based ICP-MS systems can operate using an undiluted reactive gas such as ammonia. While a reactive gas efficiently removes interferences, it is also capable of creating new interferences if not properly controlled. A true reaction cell requires the use of an active quadrupole to prevent these new interferences from forming through the creation of a mass bandpass filter, the same principle used by quadrupole mass analyzer to allow only a single mass-to-charge ratio to pass through. Cell-based ICP-MS systems using hexapoles or octapoles cannot create this mass bandpass filter.

A universal cell can be used both in the collision cell mode and the reaction cell mode, giving the best of both worlds. In some ICP-MS systems, the operator has the flexibility of operating the system in three modes all in the same method: standard mode for elements where interferences are not present; in collision mode for removal of minor interference; and in reaction mode for removal of large interferences.

One additional item before we move onto the mass spectrometer. While the ICP-MS provides a dynamic working range of 9 orders of concentration, there are times when it can be advantageous to extend the upper range of the instrument's measurement. An example would be the analysis of trace and major components in a nutraceutical sample. It can be desirable to measure the heavy metals below ppb levels while measuring major elements at the percent level in the same analytical run. Since the universal cell described above uses a quadrupole rather than a hexapole or octapole, electronic settings can be employed to extend the working dynamic range of the instrument. Using Universal Cell Technology™, Pb and Ca can be analyzed simultaneously in a nutraceutical sample without the need for sample dilution or sample rerun.

The ability of a well-designed ICP-MS to remove interferences using its standard mode, collision mode, and reaction mode can be readily seen in Figure 4.

For the Universal Cell to provide a consistent level of interferent reduction, it is most important that it be kept free from neutrals species that may exit the plasma. In Figure 5, we show the overall ion optic system of a current generation commercially available ICP-MS manufactured by PerkinElmer (NexION® 300 ICP-MS). Note that the universal cell is located at a right angle to the quadrupole ion deflector (QID). This positioning assures that the cell is fully isolated from neutrals that may exit the plasma. This results in a universal cell that will not need cleaning under typical analytical applications.

The mass spectrometer – separating ions

The mass spectrometer separates the singly charged ions from each other by mass, serving as a mass filter. Three main types of mass spectrometers are used in commercial ICP-MS systems: quadrupole, time-of-flight, and magnetic sector. For overall performance and economic value, most laboratories choose an ICP-MS with a quadrupole mass spectrometer. A quadrupole works by setting voltages and radio frequencies to allow ions of a given mass-to-charge ratio to remain stable within the rods and pass through to the detector. Ions with different mass-to-charge ratios are unstable in the cell and are ejected. To cover the full mass range, the electronics rapidly change the conditions of the quadrupole to allow different mass-to-charge ratio ions to pass through.

Under the control of the instrument software, the mass spectrometer can move to any *m/z* needed to measure the elements of interest in the sample analyzed. For example, to measure sodium, which has a single isotope at mass 23, the mass spectrometer can be set to allow ions with *m/z* = 23/1 to pass. For copper, which has an isotope at mass 63, the mass spectrometer can be set to pass ions with *m/z* = 63/1. This quadrupole is then stepped to cover the *m/z* that is appropriate for all elements to be analyzed.

While actually a sequential device, the quadrupole is capable of scanning at a rate > 5000 atomic mass units (amu) per second. This is the reason ICP-MS can determine so many different elements quickly even though only one mass passes through the quadrupole at a time.

The detector – counting ions

The ions exiting the mass spectrometer strike the active surface of the detector and generate a measurable electronic signal. The active surface of the detector, known as a dynode, releases an electron each time an ion strikes it.

The ion exiting the quadrupole strikes the first dynode which releases electrons and starts the amplification process. The electrons released from the first dynode strike a second dynode where more electrons are released. This cascading of electrons continues until a measurable pulse is created. By counting the pulses generated by the detector, the system counts the ions that hit the first dynode. The detectors used in commercial instruments are capable of a wide dynamic range using a dual mode, which includes both digital and analog modes. Rapid data acquisition rates allow the ICP-MS to be used in the analysis of nano-particles, including the counting of individual nano-particles.

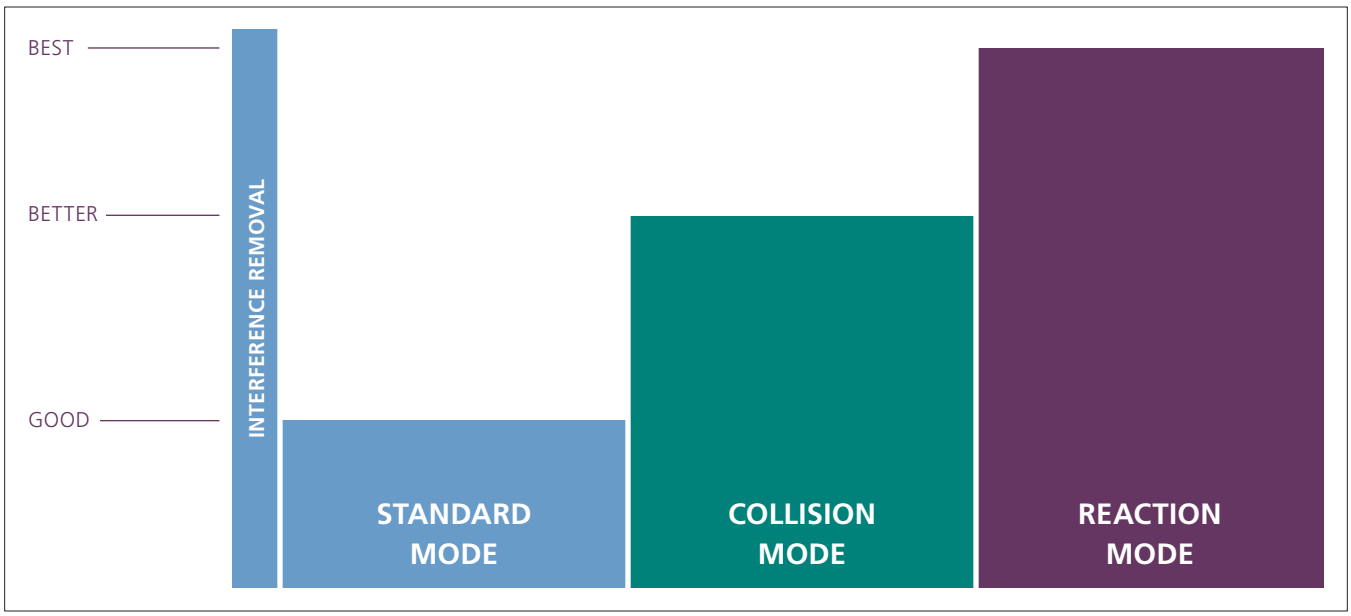

Figure 4. Interference removal using standard mode, collision mode, and reaction mode.

Hardware overview – the well-designed ion optical system

As a quick review, let's take a look at how all of the components described above come together to form the well-designed ion optical system. The argon plasma is situated immediately in front of the triple cone interface, which provides the path through which the ions generated by the plasma can enter into the quadrupole ion deflector (QID). As a reminder, the triple cone interface maintains a confined geometry of the ion beam so that no ion lenses are needed to keep the ion beam focused. The QID focuses the ions into the universal cell, while photons and neutrals travel in a straight line to exit the QID and are removed by the instrument's vacuum system. The analyte ions are preserved in the universal cell while the interferences are removed either by a collision gas or a reactive gas. Analyte ions then travel through the mass spectrometer where they are sorted by their mass-to-charge ratio, then onto the detector where they are counted. Such an ion optical system provides high analytical performance with minimal maintenance.

Data handling and system controller

All ICP-MS instruments require computers and sophisticated software to control the mass spectrometer as well as perform calculations on the data collected. Additionally, the operating parameters of the spectrometer, including proper ignition of the plasma, pressure within the high vacuum region, and the voltage applied to the detector, are to be constantly monitored by the controller, and the operator is to be alerted if any parameter falls outside of the proper working range and mass response of the instrument. All in all, the controller should monitor more than 100 separate parameters of the spectrometer.

Data handling and calculation

The software translates the ion counts measured by the detector into information that may be more useful to the operator. The ICP-MS instrument can provide data in one of four ways – semi-quantitative analysis, quantitative analysis, isotope dilution analysis, and isotope ratio analysis. Results

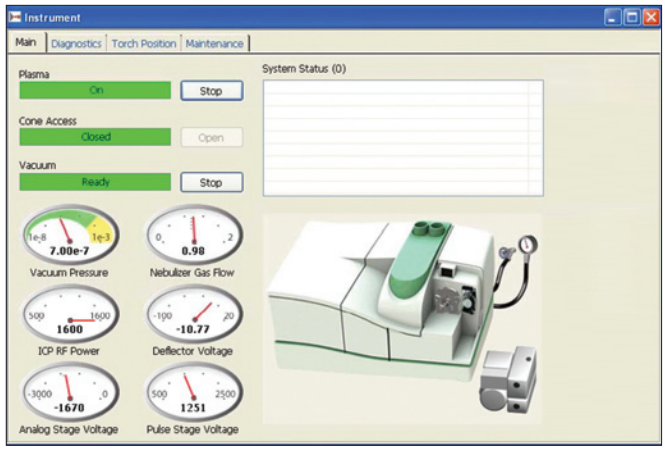

Figure 6. The dashboard that is included in the software of a well-designed ICP-MS.

can be generated using customized report formats or easily transferred to a laboratory information management system (LIMS) or other data-handling system.

Semi-quantitative analysis

For some analyses, it is not necessary to calibrate the ICP-MS for each element. After the instrument has been calibrated using a single solution containing as few as three elements, a high-quality semi-quantitative analysis for 82 elements can be performed in just a few minutes. Semi-quantitative analysis provides a fingerprint of the elements present in a sample and the approximate concentrations of each element.

This information can help determine what standards are necessary for quantitative analysis. Additionally, semi-quantitative analysis can provide valuable information on what other elements are present in a sample that could cause interferences and potentially affect the results. The software does this by comparing the measured spectrum of the unknown sample to the known isotopic fingerprints for each element and mass response of the instrument.

When a match is obtained, the element is identified and the concentration estimated by comparing the measured signal to a stored response file for that element.

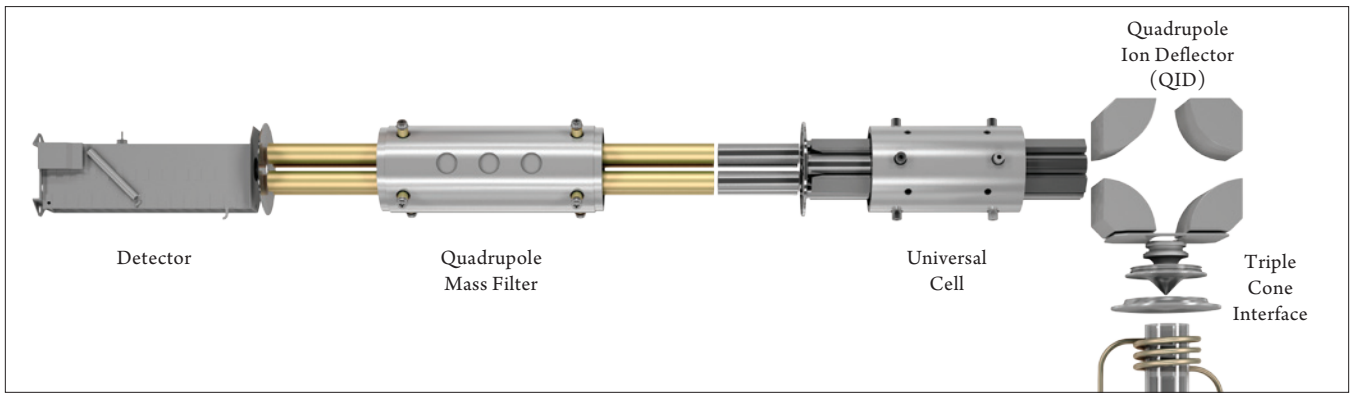

Figure 5. The ion optic path of the PerkinElmer NexION ICP-MS.

Quantitative analysis

The ICP-MS accurately determines how much of a specific element is in the material analyzed. In a typical quantitative analysis, the concentration of each element is determined by comparing the counts measured for a selected isotope to an external calibration curve that was generated for that element.

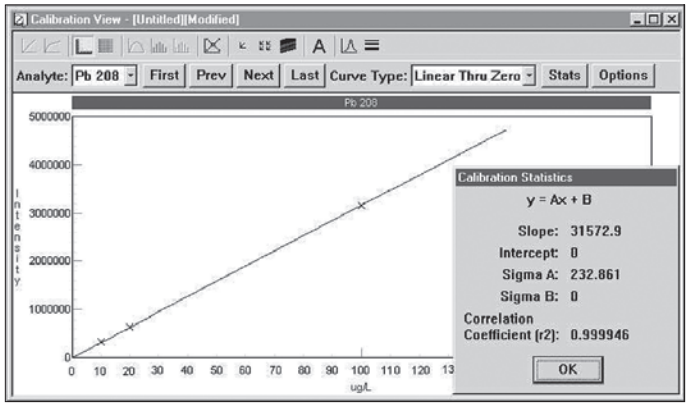

Figure 7. Quantitation calibration curve for Pb using 3 standards.

Liquid calibration standards are prepared in the same manner as used in AA and ICP-OES analysis. These standards are analyzed to establish the calibration curve. The unknown samples are then run, and the signal intensities are compared to the calibration curve to determine the concentration of the unknown. Figure 7 shows an example calibration curve for the determination of lead (Pb).

Isotope ratio

Since ICP-MS instruments measure specific isotopes of an element, the ratio of two or more isotopes can readily be determined. Isotope-ratio determinations are used in a variety of applications, including geological dating of rocks, nuclear applications, determining the source of a contaminant, and biological tracer studies.

Isotope dilution

Isotope dilution experiments can also be performed by ICP-MS. In isotope dilution, the sample is spiked with an enriched isotope of the element of interest. The enriched isotope acts as both a calibration standard and an internal standard. Because the enriched isotope has the same chemical and physical properties as the analyte element, it is the best possible internal standard. For this reason, isotope dilution is recognized as being the most accurate type of all analyses and is often used to certify standard reference materials.

Summary

ICP-MS is an ideal choice for the laboratory that is seeking the lowest possible detection limits and the highest level of productivity available. The technique is relatively free from interferences, and the interferences that do exist can often be reduced or removed through the use of a universal cell operating in either the collision mode or the reaction mode. Many laboratories find the ability to measure specific isotopes of an element invaluable.

This guide is intended as a quick general overview of ICP-MS. For those interested in more details regarding the design and operation of ICP-MS instruments, additional details can be found in the scientific literature.

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