Inductively Coupled Plasma Mass Spectrometry

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INTRODUCTION

Since the last fundamental review on inductively coupled plasma mass spectrometry (ICPMS) (1), ICPMS has continued to be a most powerful technique allowing multielemental detection over a wide linear dynamic range with very low detection limits, while also providing isotopic ratio measurement capability. In fact, a new analysis technique for trace metals has yet to be introduced that can challenge it (2). These features explain why it is not only applied worldwide to the analysis of a wide variety of matrices but its market continues to grow, unlike that of ICP optical emission spectrometry (ICP-OES), which has reached a steady state (2). Quadrupole-based (ICP-QMS) instruments constitute about 95% of that market, the remaining 5% being mostly of the magnetic sector field (SF) type, with few time-of-flight (TOF)-based instruments being sold (2). Many consider that ICPMS has matured as a technique, which appears to be supported by the fact that there have not been many significant advances in the technology recently (2), including during the period covered by this article, i.e., from October 2007 to September 2009 inclusively.

Only in March 2010 were two new ICPMS instruments introduced at the Pittsburgh Conference and Exhibition (Pittcon): the benchtop NexION 300 (ICP-QMS) by PerkinElmerSCIEX and the SPECTRO MS. The main components of the former are shown in Figure 1. The main innovations reside in (a) a triple cone interface including a hyperskimmer cone to tightly define the ion beam, (b) a miniaturized quadrupole to focus ions of a specific mass into (c) a universal cell, which can act as a collision cell, with a nonreactive gas, or as a dynamic reaction cell (DRC), with a reactive gas and bandpass adjustment, if needed (otherwise, the cell is vented). Because no ion lens is used, this ion extraction system is claimed to be “maintenance free”. Evidently, this does not include cleaning and replacing the sampler and skimmer cones regularly. On the other hand, the Al hyperskimmer does not get dirty because the diameter of its tip (1 mm) is larger than that of the skimmer (0.9 mm). The plasma view port, where an image of the whole plasma (including the top of the injector and the sampler) is obtained using a chromatic lens, facilitates the optimization of the plasma sampling position or the titration of oxygen in the plasma for the analysis of organic samples. At long last, the torch is mounted on a fully automated three-dimensional translation stage, as already provided by the other vendors. The author has only been asking SCIEX and then PerkinElmerSCIEX for this since she worked on an ELAN 250 in the mid-1980s! Why it took so long for this vendor to include this critical feature for torch alignment vs the sampling interface is beyond the author. Nonetheless, this new instrument, which retains the ELAN’s patented center-tapped load coil that eliminates any secondary discharge, is robust and well suited for the high-throughput analysis of a variety of sample types.

The SPECTRO MS is most impressive. Indeed, this double-focusing ICP-SFMS instrument with the Mattauch–Herzog geometry (Figure 2) focuses all separated ions onto a new direct charge detector, whose 4800 channels allow the simultaneous detection of the entire mass spectrum. Each channel is composed of an array that can process a wide range of signals. It also features a five-component ion optic, which was designed for efficient ion transport while filtering out electrons, photons, and neutrals. It will be interesting to see the impact of this instrument on the range of ICPMS applications. Indeed, despite its small share of the market, ICP-SFMS has resulted in an extensive and rapidly expanding body of literature (3). Simultaneous detection, which eliminates spectral skew and allows correlated noise to be overcome by ratioing two signals (4), of the whole mass spectrum on a single multichannel detector combined with high mass...
resolution is an attractive approach that has been desired for some time (5). If there is no blooming-type problem between channels, then it may supplant multicollector (MC) ICP-SFMS, where only a few isotopes can be detected simultaneously and the detectors can have different response times. So, stay tuned until the next fundamental review, as some reports on its performance should have been published by then!

In any case, whatever the type of mass spectrometer, ICPMS is not only increasingly used in interdisciplinary studies but has become an invaluable tool for a broad range of disciplines, including health, forensic, material, and nuclear sciences, to name a few. As a result, at least a thousand papers involving ICPMS are now published each year, the majority of which deal with applications. Review articles that survey the relevant literature in
specific areas then become invaluable to the ICPMS users in those areas, even more so if they do not have time to continuously monitor the literature or do not have access to many journals.

On the other hand, because the technique is considered mature, the number of fundamental studies and significant advances dwindles, despite the fact that there is still room for improvement. Indeed, the susceptibility of ICPMS to matrix effects often complicates analyses by requiring either more time-consuming calibration strategies then a simple external calibration (EC) or additional sample pretreatment (to eliminate the source of the problem). Indeed, at least internal standardization (IS) must usually be carried out, if not the method of standard addition (MSA) or isotope dilution (ID), which require spiking each sample. If these effects were fully understood, then efficient remedies could be devised, which would further expand the applicability and usefulness of ICPMS. Hence, despite the fact that ICPMS has been around since the early 1980s, it still is not as free of chemical interference as originally forecasted. Similarly, although different strategies can be used to resolve or eliminate spectroscopic interferences, no single approach is suitable in all cases.

The objective of this fundamental review article, which follows up on the previous one (1), is to critically review significant developments in ICPMS from October 2007 to September 2009 inclusively. So, it does not provide a comprehensive coverage, although several references to review papers are included. To select the most significant or representative publications (at least, in the view of the author), selected peer-reviewed journals were systematically perused: Analyst, Analytical Chemistry, Analytical Chimica Acta, CRC Critical Reviews in Analytical Chemistry, Analytical and Bioanalytical Chemistry, Applied Spectroscopy, Applied Spectroscopy Reviews, International Journal of Mass Spectrometry, Journal of Analytical Atomic Spectrometry, Journal of the American Society for Mass Spectrometry, Metallomics, Microchemical Journal, Microchimica Acta, Rapid Communications in Mass Spectrometry, Spectrochimica Acta, Part B, Talanta, and Trends in Analytical Chemistry. A recurrent observation from the previous review (1) is that the huge number of papers published each year makes it increasingly difficult for editors and referees to ensure the novelty and significance of manuscripts being published. Too many authors review only the recent literature, thereby completely missing seminal work that was carried out in the early days of ICPMS or on the related ICP-OES technique. At the very least, several literature searches, i.e., for each of the keywords of a manuscript, should be done to increase the likelihood that the publication is really original and significant. With the many search engines available, there is really no excuse for not doing so!

Conferences. New ICPMS instruments are usually launched at Pittcon, which is held annually in the U.S.; it was in Orlando, Florida, in March 2010 and will be in Atlanta, Georgia, March 8–13, 2011 (www.pittcon.org). However, it is a huge event with numerous parallel sessions and an enormous exhibition on all sorts of scientific instrumentation held concurrently. In contrast, the Winter Conference on Plasma Spectrochemistry, which is held in the U.S. and Asia on even years and in Europe on odd years, is largely focused on ICPMS, and its exhibition includes all ICPMS vendors. It was held in Fort Myers, Florida, in January 2010 and will be in Chengdu, China, November 26–30, 2010 (for information, contact houxiandeng@yahoo.com.cn), and in Zaragoza, Spain, January 30–February 4, 2011 (www.winterplasmazaragoza2011.es). Although, several years ago, the U.S. version used to only have a single session so that nothing could be missed, it now has poster sessions in parallel with oral presentations on several days and the format is exhausting, as this 6 day event starts at 8 a.m. ends at 6:30 p.m. (excluding social events in the evening) each day, with barely an hour for lunch. Numerous short courses instructed by gurus in the field are also held on the mornings, afternoons, and evenings of a few days immediately preceding the conference. Foreigners should thus consider arriving well prior to the event to have some time to overcome jet lag!

Other noteworthy North American conferences that feature a significant atomic spectroscopy section where ICPMS is prominent are held annually. The 37th annual meeting of the Federation of Analytical Chemistry and Spectroscopy Societies (FACSS) will be in Raleigh, North Carolina October 17–21, 2010 (see http://facss.org). This 4 day event usually does not have more than one session on atomic spectroscopy being held in parallel with sessions on other fields (molecular spectroscopy, mass spectrometry, etc.), although some relevant workshops may be held concurrently. A more intimate meeting (whose attendance is around 150) is the 56th International Conference on Analytical Sciences and Spectroscopy (ICASS), which will be held in Edmonton, Alberta, August 15–18, 2010 (see http://www.icass.ca). Likely because of its smaller size, this 3 day event is the most “civilized” of the above-mentioned conferences while providing the most for its registration fee. Not only is the latter lower than that of FACSS and significantly less than that of the Winter Conference, but lunches (and sometimes breakfasts) are usually included to increase the networking opportunities! It is also more relaxed than the other meetings. For instance, it includes 40 min coffee breaks in the morning and the afternoon and a 1.5 h lunch. Furthermore, oral sessions typically start at 9 a.m. and end around 5 p.m. daily, when dedicated poster sessions are held for 1–2 h, with refreshments provided.

Book and Reviews. Only one book containing a significant section on ICPMS was published and reviewed during this review period. “Inorganic Mass Spectrometry: Principles and Applications” authored by Johanna Sabine Becker and published by John Wiley & Sons, Ltd. in February 2008 (ISBN 978-0-470-01200-0) was reviewed positively by two experts (6, 7).

On the other hand, as mentioned earlier, several articles reviewed different application areas of ICPMS, involving the analysis of (1) environmental samples (air, water, soil, plants, geological materials, airborne particulate matter, etc.) (8–10); (2) industrial products including metals, chemicals (organic, inorganic, and petroleum products) and advanced materials (polymers, composites, glasses, ceramics, catalysts, etc.) (11, 12); (3) clinical and biological materials, food and beverages (including wine) (13–15); (4) nanoparticles in bioanalytical applications (16, 17); and (5) paper documents (18) or focusing on the determination of (1) radioisotopes and transuranic elements (19, 20); (2) the isotopic composition of zinc and its use in the biogeoosciences (21); (3) wear metals in oil (22); and (4) natural or added element tags in immunoassays, metallokins, epigenetics, and clinical diagnosis (23–27).

Advances in instrumentation, methodology, and understanding of ICPMS were also reviewed (28, 29). A lowering of detection
limits is the most common criterion used to assess the extent of improvement in ICPMS performance upon a change in instrumentation or methodology, while quantitation limits are more relevant in the case of specific applications. Yet, several definitions can be used for the latter, from the most frequent 10σblank to the lower limit of the calibration curve and even uncertainty approaches (30). These different definitions, which vary in terms of complexity, each have advantages and limitations that are thoroughly discussed in a clearly written tutorial article (30). All ICPMS users who are not familiar with the different possibilities should attentively read this paper, as it will enable them to select the most relevant method, based on the wealth of information that can be derived from the calibration curve (30).

Speaking of calibration, both “calibration” and “external calibration” are used in the literature, which can be confusing, even more so if the expression is not used correctly (31). The definitions set by IUPAC (International Union of Pure and Applied Chemistry) should be followed to eliminate this dilemma, and the extent of matrix matching of the standards to the samples should be specified (31). In the case of complex matrixes, a multivariate calibration, principal component analysis (PCA) and partial least-squares regression in particular, may be worthwhile to correct for spectroscopic and nonspectroscopic interferences (32).

**SAMPLE PREPARATION**

**Reviews.** The large number of applications and the wide variety of sample types translate into a plethora of sample preparation methods. Again, review articles are useful to put the various possibilities in perspective and help select the most appropriate method for a given application, taking into account constraints in terms of available equipment, reagents, etc. For instance, food samples may be prepared in different ways prior to the determination of metals. In addition to conventional methods, such as dry ashing and acid digestion with and without the assistance of microwave energy, alternative strategies are increasingly used to reduce reagent consumption and the time required for sample preparation (33). In particular, direct solid analysis, using laser ablation (LA) for example (to which a section is devoted later in this fundamental review), not only allows the analysis of microsamples but can also be used for fast screening (33). A more recent sample treatment is ultrasonic-assisted enzymatic digestion, which relies on ultrasounds and enzymes to accelerate solid–liquid extractions prior to either elemental determinations or speciation analysis (34). With careful data interpretation to avoid common errors (such as wrong sample size), this methodology can be relatively rapidly applied, as explained in a detailed guide (34).

Many sample treatment techniques, including extractions, reactions, and digestions, can be accelerated and made more efficient using microwave energy (35). Furthermore, performing this sample treatment online with the detection system is advantageous, as it reduces solvent consumption, sample contamination, and as a result, usually reduces the overall analysis time, which increases sample throughput (35, 36). Moreover, ICPMS sensitivity and selectivity can be improved using online preconcentration and/or separation procedures involving solid phase extraction (SPE), liquid–liquid extraction, cloud point extraction, microdialysis, chemical vapor generation, or electrochemical deposition (36,37).

However, online SPE methods can suffer from progressive compaction of the solid-phase extractant, which increases back-pressure and degrades reproducibility. Pumping the sample through one end of the SPE material and then pumping the eluent through the opposite end can circumvent this problem, as is typically carried out when using an automated PerkinElmer FIAS unit to carry out SPE (38). However, this does not compensate for degradation of the SPE material. One way around this shortcoming is bead-injection (BI) analysis, where new sorbent is automatically loaded for each assay (39).

Miniaturization is relatively straightforward using microfluidic systems based on the lab-on-valve (LOV) approach, where a syringe pump is used to move the sample into a holding coil for reaction, extraction, sorption, etc., and then pump the product to the ICPMS sample introduction system for detection (40). In contrast to the lab-on-a-chip platforms, the LOV approach does not require any chip redesign to enable the implementation of various procedures, such as SPE, chemical vapor generation, chemical derivatization, precipitation or coprecipitation, and BI (40).

**Original Approaches.** The low detection limits of ICPMS open the way to in vivo monitoring, although some precautions must be taken. For example, desalting of the saline microdialysate of the extracellular fluid of anesthetized rats is necessary prior to delivery to ICPMS to prevent drift from salt build up on the sampler and skimmer cones (41). This could be carried out online, following complexation of analytes by ethylenediaminetetraacetic acid (EDTA), using a carbohydrate membrane desalter that acted as a cation exchanger and quantitatively removed Na⁺ while the EDTA anionic complexes of the analytes were preserved (41). This essentially allowed real-time determination of analytes present at milligram per liter levels, such as Ca and Mg. On the other hand, analytes at subnanogram per milliliter levels, such as Cu, Zn and Mn, required a 10 min accumulation prior to analysis to enable their detection by ICPMS (41). An alternative to the latter, is to use a 10 cm long, 0.76 mm i.d. piece of nonfunctionalized poly(vinyl chloride) tube for SPE (42). Using phosphate buffer to adjust the pH of the dialysate to 8.0 allowed quantitative adsorption of analytes, which following a 12 min accumulation could be eluted with 0.5% HNO₃ (42).

An electrodialyzer equipped with a cation-permeable membrane can also be applied to the determination of trace elements in concentrated KOH solution following their complexation with EDTA (43). For very low concentrations, an alternative approach is to use a liquid membrane system (44). It consists in a cell made of two concentric beakers, an external one containing 48 mL of sample (whose pH is maintained at 5.5 with 0.43 M acetate buffer) and an internal one containing 8.5 mL of 2 M HNO₃ receiving solution, over which 7 mL of liquid membrane is spread (44). This liquid membrane, which carries metal ions from the sample to the receiving solution, consists of a complexing agent in kerosene. With the use of 0.144 M DEHPA (di-(2-ethylhexyl) phosphoric acid), extraction efficiencies ranged from 44% (for Cd) to 78% (for Cu) after 9 h of extraction, depending on the affinity of analytes with DEHPA (44). This simple approach minimizing sample manipulation and thus contamination, with limited reagent consumption and waste generation. On the
other hand, optimization is still required (in terms of a more effective complexing agent) to enable the application of this approach to truly multielemental quantitative analysis of seawater.

The determination of the platinum group elements (PGEs) is notoriously difficult in geological and environmental samples because of the low levels of PGEs involved and the formation of interfering polyatomic ions. For example, ZrO\(^+\), Yo\(^+\), SrO\(^+\), TaO\(^+\), HfO\(^+\), ArZn\(^+\), and ArCu\(^+\) interfere with major isotopes of Pt, Pd, and Au. Cloud point extraction, which is a solvent-free approach providing high preconcentration factors, can be used to circumvent these difficulties (45). For example, an interference-free 100-fold preconcentration can be achieved using N\(_2\)-dihexyl-N\(^-\)-benzoylthiourea, which selectively forms very stable complexes with the analytes that are then extracted into nonionic surfactant Triton X-114 upon heating the solution (45). The surfactant-rich phase is decanted, washed with water, and dissolved in MeOH containing 1 M HNO\(_3\) prior to analysis by ICPMS (45). The approach is effective, as long as the original sample digest is adjusted to 10% v/v HCl and does not contain more than 2% v/v HNO\(_3\) (45). The process can be accelerated using microwave energy. For instance, 10 min of microwave irradiation was sufficient to extract the Rh, Pd, and Pt complexes with 2-mercaptopentanoic acid from pharmaceutical products into Triton X-100, which was decanted and dissolved in 1 M HCl for ICPMS analysis (46). In such extractions, the oxidation state of analytes is important, as some forms (for example, Pt(IV)) may not be extracted as efficiently as others (Pt(II)), prereduction (such as with 0.1% m/v SnCl\(_2\)) then being recommended (46). Such considerations are even more important when speciation analysis is to be carried out.

Corrosion processes can be studied using a microflow-capillary system that continuously cycles 620 \(\mu\)L of corrosive solution over the surface of a sample, with 20 \(\mu\)L aliquots being injected into ICPMS every 115 s (47, 48). If a potential from \(-400\) to +1000 mV is applied to the sample while it is exposed to corrosive solution, the simultaneous acquisition of electrochemical information with the temporal and elemental composition data afforded by ICPMS allows a characterization of the corrosion process heretofore unavailable (48). The flow injection (FI) sampling of the corrosive solution minimizes salt deposition on the interface cones, especially with 0.1 M NaCl, which would otherwise translate into analyte signal drift (47).

To improve reproducibility while avoiding sorbent compaction during SPE, an alternative approach was used, where superparamagnetic Fe-based nanoparticles that were modified with poly(acrylic acid) could be maintained at a fixed position between frits with the use of an external 3000 G magnetic field (49). For 20 \(\mu\)L sample injections, sharp and essentially symmetrical elution peaks resulted, with the whole cycle (i.e., column conditioning, simultaneous sample loading and matrix separation, and elution) completed within 5 min (49). However, the preconcentration factor that can be achieved was not specified. The approach would also not be suitable for the determination of paramagnetic elements.

Instead of doing everything online, part of the process can be carried out off-line to minimize instrument usage time. This is particularly attractive in combination with the sampling step. For example, commercially available chelating columns can be attached to a syringe, which is used in the field to collect seawater (50). The chelating resin adsorbs trace metals whereas major elements, such as Na, Mg, Ca, and K, are not retained to the same extent and are thus simultaneously separated. Back in the laboratory, on-line elution of the analytes to ICPMS is carried out with 2 M HNO\(_3\) (50).

Some improvements can also be made to conventional digestion methods. For example, NH\(_4\)F successfully replaced HClO\(_4\) and HF in the multistep dissolution of lichen, soil, and basalt with HNO\(_3\), NH\(_4\)F, and H\(_2\)O\(_2\), thereby avoiding the safety issues associated with HClO\(_4\) and HF (51). Given the cost of HClO\(_4\) and HF and their toxicity and corrosive nature, this is definitely an approach worth further consideration! Another interesting approach that is useful in the case of biological tissues (fish, bovine muscle, and bovine liver), involves solubilization of 75 mg of sample in 1 mL of 50% (v/v) tetramethylammonium hydroxide (TMAH) solution within 12 h without heating the samples (52). This approach has the advantage of not requiring constant monitoring of the digestion, allowing a hundred samples (or more) to be processed in parallel. It is also applicable to the determination of volatile elements, such as Hg, which may be lost upon heating (53). The solubilization time may be reduced to less than an hour by heating the samples to 50–60 °C (52). In any case, dilution to 10 mL with a mixture of 0.5% (v/v) HNO\(_3\) and 0.01% (v/v) Triton X-100 was then required to ensure stable analyte signals during nebulization in ICPMS (52). Nonetheless, despite the fact that 75 mg is less than the minimum amount recommended by reference material producers, accurate results were obtained for many elements, including Cr, which however required hydrogen in a DRC to alleviate the 40Ar12C interference (52). It would be interesting to see if this approach could be used for the analysis of carbon nanotubes, which are difficult to dissolve in acids, requiring more acid and longer digestion time than biological materials, even if microwave energy is applied (54). In fact, if a microwave digestion system is not available, then a dry ashing pretreatment is necessary prior to acid digestion (54).

A “green” alternative to acid digestion is microwave induced combustion, where a pellet of sample powder is placed in a quartz holder along with filter paper that is wet with NH\(_4\)NO\(_3\), which is then placed in a quartz vessel containing 0.1 M HNO\(_3\) (55). Following pressurization of the vessel with O\(_2\), it is placed in a microwave oven and irradiated 5 min at 1400 W. Finally, following 20 min of cooling, the resulting solution may be diluted as needed prior to analysis (55). In addition to not requiring concentrated acids, this simple approach yielded clear and transparent solutions with <0.5% residual carbon content when applied to biological (seafood) materials (55). Even if a furnace is used instead of a microwave oven, the simplicity of this method combined with the few reagents needed leads to lower procedural detection limits than with other sample preparation methods (56).

A variation of the vapor phase decomposition approach that is widely used in the semiconductor industry to analyze the surface of silicon wafers was proposed as an alternative to LA-ICPMS for depth profiling, to get around the limited availability of matrix-
HNO₃ was added and the whole 6 µL was removed with a pipet and diluted to 1 mL with more 1% HNO₃. This solution was then analyzed by ICPMS with matrix-matched standards and IS (57). The removal depth was varied by changing the contact time and the concentration of the etching solution: 500 Å with 0.5% HF for 10 s, 150 Å with 0.25% HF for 5 s, and 70 Å with 0.1% HF for 5 s. However, as the removal depth was decreased, the number of elements that could be detected also decreased, commensurate with the reduced absolute amount of material removed (57).

**INSTRUMENT DEVELOPMENT, CHARACTERIZATION, AND OPTIMIZATION**

**Direct Sample Introduction.** The direct measurement of carbon isotope ratio in gases can be done by connecting the sample gas cylinder to the ICP torch using PTFE tubing and a one-flow restrictor, which regulates the flow without the need for a mass flow controller that might induce isotopic fractionation (58). A new inexpensive gas converter apparatus was developed for the real time analysis of airborne particulate matter (APM), which is important to enable the study of APM kinetic behavior in ambient air (59). The apparatus consists of two concentric tubes: a porous silica tube in which the air sample flows, which is in a borosilicate glass tube in which a counterflow of Ar is introduced. Because of the difference in partial pressures in the two tubes, the gas molecules in air are exchanged with Ar, thereby allowing APM to be carried to the plasma with Ar (59). To increase the gas exchange efficiency, three gas converters were used in parallel to allow 650 mL/min air to be introduced and exchanged using 7 L/min Ar sweep gas, with APM of all sizes being directly introduced into the ICP torch injector (59). This however translated into a noisy signal, with many spikes, indicative of a variety of coarse particles reaching the plasma. If a particle size selector were also used at the inlet of the gas converter, kinetic studies related to specific size would become possible, although quantification is problematic, as standards with known elemental concentrations, chemical composition, and particle size distributions are required.

**Nebulization.** The sample throughput can be doubled with an Elemental Scientific FAST sample introduction system (Figure 3), which uses a diaphragm pump to instantaneously fill a sample loop, the content of which is then injected into an acidic carrier stream (60). The latter, which is pumped by a peristaltic pump, is merged with internal standard solution before reaching a low-flow, PFA-FAST microconcentric nebulizer that is inserted in a Peltier-cooled, baffled, glass cyclonic spray chamber (60). While the injection volume is large enough to result in a steady-state signal, the discrete injections effectively minimize salt build up on the cones. Furthermore, memory effects and washout times are minimized because the sample solution is only in contact with PTFE (i.e., never flows through peristaltic pump tubing) (60), unlike with conventional FI where a peristaltic pump is used to load the sample into the sample loop. Hence, compared to conventional FI combined with a pneumatic cross-flow nebulizer and Scott double-pass spray chamber, better precision and accuracy are achieved, with lower detection limits and reduced sample consumption (61). One exception is Hg for which significant carryover resulted because the FAST sample loop is not really rinsed (i.e., introduction of the next sample rinses the loop) (60). Nonetheless, the high throughput afforded by the FAST system makes it popular with ICPMS vendors, which often use it during demonstrations or while analyzing samples for potential new customers.

Another way of reducing memory effects while increasing sample throughput and minimizing sample consumption is the torch-integrated sample introduction system (TISIS), which is a total-consumption microsample introduction system (62). It consists of an 11 cm² single pass spray chamber that is wrapped with heating tape and maintained at 70 °C, as heating the chamber, which enhances aerosol evaporation, increases both transport efficiency and the plasma thermal characteristics (63). The chamber has a lateral port for the introduction of Ar sheathing gas to prevent the aerosol from striking the chamber walls, as sudden evaporation of droplets upon contacting the hot surface and renebulization of deposited analytes can result in signal spikes, which degrade precision and detection limits (62). A micronebulizer, such as PFA-ST, is fitted to the chamber base using a Teflon adapter, and the chamber is directly connected to the injector of the ICP torch (62). Because introducing the sheathing gas increases both analyte sensitivity and oxide formation, the flow rate resulting in significant analyte signal increase with limited oxide formation must be selected (0.1 L/min) (62). Similarly, a compromise nebulizer gas flow rate is required. Nonetheless, total consumption could be achieved with up to 80 µL/min sample uptake, as no condensation was observed on the chamber walls, which translated in improved sensitivity and detection limit compared to those achieved using sample introduction with a PFA-ST microconcentric nebulizer and a cyclonic spray chamber (62).

Such high-efficiency sample introduction systems, another example of which is the APEX (which consists of a heated spray chamber combined to a Peltier cooler), can be used to compensate for the loss of sensitivity that results from increasing the mass resolution of SFMS instruments (64).

In any case, all noise sources must be minimized if the lowest possible detection limits are to be attained, including the pulsating effect of the peristaltic pump, which is customarily used to supply a constant flow rate of sample solution to the nebulizer and, in
addition, to continuously empty the drain port of the spray chamber. However, doing the latter creates a segmented gas−liquid stream, which may significantly change the internal volume of the spray chamber, therefore translating in signal pulsing. Such an effect may be minimized by using a separate pump than that used for sample introduction to pump the drain. Its flow rate may then be adjusted to obtain the smallest volume of gas required for a segmented flow (65).

**Plasma Processes.** Progress was made in simulating the kinetics of the vaporization of solute particles in the plasma as a function of ICP operating conditions, electron and gas temperatures, spatial location in the ICP, as well as the diameter, chemical composition, and size distribution of the particles (66). Such simulations predict that only particles with a diameter smaller than roughly 0.4−0.6 μm can be completely vaporized in the plasma region that is sampled in ICPMS, in agreement with previous LA results that used an impactor to select the range of particle sizes reaching the plasma (ref 66 and references therein). However, the spatial resolution at which plasma fundamental parameters can be simulated is still insufficient and would require additional computing resources. Such simulations would be useful to predict results, especially in the cases of difficult, expensive, or dangerous experiments.

The injection of 1−10 monodisperse droplets of 35−67 μm diameter per second into the ICP allowed a study of the effect of desolvation and atomization through simultaneous end-on optical emission spectroscopy measurements of hydrogen, analyte, and Ar lines, which confirmed the beneficial effect, through improved heat conduction, of the hydrogen produced during desolvation (67). It also revealed that relatively small differences in analyte mass can significantly change the local plasma temperature during atomization, which would translate in variations in analyte signal, and that the atomization of a major element may negatively affect that of a nearby trace element (67).

The ICP quartz torch temperature is another parameter that is worth monitoring. Indeed, operating conditions should be selected so that it is as high as possible to minimize dissipation of plasma energy, thus leaving as much as possible for the analytes without reaching a critical temperature where divitification occurs, as this ultimately leads to torch melting. Infrared thermography can be used to quickly obtain a spatially resolved distribution of torch-wall temperature, in a nonintrusive way, while the plasma is operating (68). Such measurements revealed that a conventional Fassel-type torch exhibits an inhomogeneous temperature distribution, with clearly defined stress features that depends on the position of the plasma in the torch (68). Hence, infrared thermography constitutes a new tool for plasma diagnostics, which should also be very useful for the optimization of torch design.

**Plasma Sampling Processes.** A direct simulation Monte Carlo algorithm was applied to model the small region where hot plasma gas flows into the sampler, with good agreement with fluid dynamics equations (69). In addition, the simulation indicated that the formation of a boundary layer reduces the total flow rate through the sampler by about 15% compared to the ideal value predicted by the approximate hemispherical sink model and that this reduction is roughly independent of temperature over the range 4000−7000 K (69). A different computer simulation yielded velocities in agreement with experimentally determined values in the 6 mm region upstream of the sampler (70). In contrast, the values obtained with a modified hemispherical sink model were as much as 30% different from experimental values (70). Such models are thus useful to predict the flow properties upstream from the sampler under a range of plasma operating conditions.

The effect of the sampler on analyte ion and atom distributions was ascertained by comparing images obtained by using planar laser-induced fluorescence of the ICP with and without the sampling interface (71). Placing the ICP in contact with the sampler significantly decreased the density of singly charged ions 1−2 mm upstream of the sampler but increased it 7−8 mm downstream from the load coil (71). The decrease in ion density near the sampler is partially due to acceleration of the plasma by the vacuum in the interface. However, the presence of the interface decreased the inferred plasma temperature 4−9 mm downstream from the load coil. The most plausible explanation for an increase in the number of singly charged Ba ions despite this lower plasma temperature is a shift in the population of doubly charged ions toward singly charged ones (71). This, in turn, suggests that the ICP may efficiently produce doubly charged ions if the sum of the first and second ionization energies of the analyte is smaller than the first ionization potential of argon. Indeed, no similar increase in singly charged ion density was observed for Sr and Ca, for which the sum of ionization energies is greater than the ionization potential of Ar (71).

High-resolution laser-excited fluorescence spectroscopy was used to probe Ca ions and Ar atoms downstream from the sampler and revealed that Ca ions had a terminal velocity 5−6% higher than Ar atoms despite their very similar mass (72). This difference could be reasonably accounted for using a computational model, which indicated that gradients in electron density and temperature within the interface resulted in an ambipolar electric field that slightly accelerated ions in addition to the acceleration caused by the vacuum in the interface (72).

**Ion Detection.** ICPMS is frequently used for the detection of transient signals, such as those generated by FI, capillary electrophoresis (CE), and LA to name a few approaches. Such measurement imposes constraints on the number of elements that can be simultaneously determined by sequential-type mass spectrometers, depending on the intensity and width of the transient signal, which are thoroughly discussed in a review article (73). Some means of controlling or, at least, monitoring the dynamic processes occurring in the plasma is required to obtain accurate results. Although they can be compensated by using isotope ratios, care should be taken since, even with multicollector ICPMS, which allows the simultaneous detection of several ions on different detectors, drifting isotope ratios may be observed during transient signals, thereby limiting the precision and accuracy of results (73). Only simultaneous detection over a planar detector would obviate these limitations, as was demonstrated with a Faraday-strip array detector installed on a Mattauch−Herzog mass spectograph with an ICP ion source (74, 75). This detector provided a better duty cycle than sequential-type mass spectrometers, resulting in better detection limits and precision because all isotopes could be monitored for a longer time; yet, total analysis time was shorter, thus reducing sample consumption (74, 75). Furthermore, because different ions are truly detected simulta-
neously on the same detector, correlated noise can be reduced by ratioing signals, and spectral skew is eliminated, allowing accurate analysis of transient signals (74). However, this array detector does not currently provide full mass range coverage. In fact, the mass range depends on the flight radii of ions in the magnetic field. Hence, while the two Li isotopes cannot be measured simultaneously, 34 amu can be acquired simultaneously from m/z 227 (Ac) (75).

Whatever the type of instrument and detection system, a multivariate optimization is wiser than varying one condition at a time, especially when multielemental analysis is to be carried out, because many operational parameters are interdependent, such as the nebulizer gas flow rate and radiofrequency power. Such procedure was carried out to optimize 21 operating conditions (including plasma positioning, ICP gas flow rates and MS conditions) for maximum ICPMS sensitivity for 83 isotopes (70). It involved four steps: (i) a Simplex optimization was used to provide the initial set of experiments; (ii) PCA was applied to the signal intensities generated by that initial Simplex in order to identify a multicriteria target function; (iii) a modified Simplex optimization was then carried out to find conditions maximizing the target function; finally, all experiments performed in sets (i) and (iii) were used in a partial least-squares regression model to assess the effect of each factor on the response (76). With the use of this approach, the improvement in sensitivity ranged from 2 to 12 times that observed with conventional univariate optimization, with similar or improved detection limit by up to a factor of 6 (76).

**SPECTROSCOPIC INTERFERENCES**

The combination of computational methods with accurate m/z measurements by double focusing ICP-SFMS allows an evaluation of the likely origin of polyatomic ions, including ions that are not very abundant from the ICP, and of their electronic, vibrational, and rotational energy states (77). Such fundamental information is useful, as it may help figure out ways of eliminating these spectroscopic interferences. For example, N$_2^+$ and N$_3^-$ are two polyatomic ions that are observed in ICPMS, especially with the common 1% HNO$_3$ matrix. Similarly, HCOO$^-$, CO$_2^-$, and CO$_3^-$, as well as H$_2$CO$^+$ and HCOH$^+$ come from organic components and dissolved CO$_2$. Computational methods are invaluable for taking into account isomers (HCO$^+$ and COH$^+$; H$_2$CO$^+$ and HCOH$^+$) that cannot be mass resolved experimentally. The energies, structures, and partition functions of the ions, which were determined by calculations based on spin-restricted open shell second order perturbation theory and coupled cluster theory, were combined with experimental data to yield a gas kinetic temperature. In all cases (N$_2^+$, N$_3^-$, HCOO$^-$, CO$_2^-$, CO$_3^-$, H$_2$CO$^+$, and HCOH$^+$), this temperature was significantly less than that in the ICP, which likely indicates that at least a portion of these ions was formed in the interface or extraction region (77).

Ab initio theoretical calculations of the potential energy surface of reactions were similarly used to support the effect of collision/reaction cell (C/RC) conditions (in particular, hexapole rf amplitude, proportions of H$_2$ and Ar, and hexapole pressure) on the reactions of ArO$^+$ and ArOH$^+$ with H$_2$. However, they indicated the formation of ArOH$^+$ from ArO$^+$ in the C/RC (78). In fact, even under conditions where the reaction of ArO$^+$ with H$_2$ had maximized and where ArOH$^+$ could be removed faster than it was formed from ArO$^+$, the level of ArOH$^+$ remained high because of the large amount of ArO$^+$ that was there to begin with (78). This is problematic for the measurement of the Fe isotope ratio with high precision using multicollector ICPMS (MC-ICPMS) with a hexapole C/RC.

Moreover, using a collision cell does not necessarily preclude having to apply a correction equation. For example, when performing the determination of Fe at subnanomolar levels in seawater using $^{54}$Fe$^+$, following preconcentration by Mg(OH)$_2$ coprecipitation, the NH$_3$ reaction gas that was used in a DRC to decrease the background (in particular, from $^{38}$Ar$^{40}$O$^+$ and $^{40}$Ar$^{23}$Na$^+$) did not reduce the $^{54}$Cr$^{39}$ isobaric interference, which still required a correction equation (79). Care should also be taken to check that no new interference is created in the C/RC at each m/z measured for the correction. An example is $^{81}$Br$^+$ when H$_2$ is used, which leads to an erroneous correction of $^{40}$Ar$^{35}$Cl$^+$ interference on $^{75}$As$^+$ through overestimation of $^{82}$Se$^+$ and, in turn, the $^{77}$Se$^+$ contribution on $^{97}$Ar$^{37}$Cl$^+$ (80). It also precludes the determination of Se in volcanic soil digests using $^{82}$Se$^+$, as Br is present in almost all such soils (81). In fact, for such application, monitoring $^{78}$Se$^+$ is recommended along with both a H$_2$-pressurized C/RC and 2% v/v methanol in the sample solutions (81). Methanol not only improves the sensitivity for Se but also reduces argides, presumably through competitive carbide formation (81). If Se is introduced into the plasma using hydride generation, then $^{76}$Se$^+$H$^+$ and $^{77}$Se$^+$H$^+$ can be formed, which interfere with $^{77}$Se$^+$ and $^{78}$Se$^+$ and require correction equations if these Se ions are monitored (82). This problem is even more important if a He/H$_2$-pressurized C/RC is also used, as additional hydrides can then be formed in the C/RC (82). However, a He/H$_2$-pressurized C/RC was reported to be more efficient than SFMS, even at high mass resolution, at alleviating the spectroscopic interference from argon dimers (82). Even with $R = 10,000$, the determination of Se using either $^{80}$Se$^+$ by ICP-SFMS is not possible because of the severe interference from $^{40}$Ar$^{40}$Ar$^+$ and using $^{82}$Se$^+$ is precluded by spectroscopic interference from $^{81}$Br$^+$H$^+$ in Br-containing samples (64).

Whether a C/RC is used or not, mathematical corrections can be made using different algorithms, which can lead to very different combined uncertainties, as the efficiency of each approach depends on both the number of spectroscopic interferences at a given m/z and the proportions of analytes and interfering agents (83). As all correction equations automatically increase the combined uncertainty, no matter how effective each approach is, an uncertainty budget analysis is useful to select both the best correction approach and the most appropriate analyte isotope for a given analysis (83). In some cases, such as the determination of Rh, Pd, and Pt in road dust, the robustness of the correction approach can be increased by removing substantial amounts of the interfering agents through partial leaching (in this case, with 0.35 M HNO$_3$) prior to microwave digestion of the samples (83). This simple approach can be advantageous in all cases where the analytes are relatively immobile, whereas major matrix components are easily solubilized.

Using a 4 mL/min He flow in a C/RC was reported to efficiently remove matrix-based interferences (such as $^{40}$Ca$^{16}$O$^+$ and $^{40}$Ar$^{23}$Na$^+$ on $^{56}$Ni$^+$ and $^{62}$Cu$^+$) while reducing background.
equivalent concentrations 10-fold compared to those achieved with a vented cell (84). Furthermore, despite the about 40% carbon content of rice digests, no carbon-based polyatomic interference was observed under these conditions (84). On the other hand, because the C/RC also reduced ion transmission and the signal-to-noise ratio, thereby degrading detection limits, it was not used for the semiquantitative analysis of rice grains digests, as the maximum number of elements had to be determined to allow distinction of the different rice genotypes through PCA (84). The results also indicated that semiquantitative analysis, which allowed monitoring 73 elements over the whole mass range, provided a stronger discrimination power than a full quantitative analysis, with only 21 elements determined, despite being far less time-consuming (84).

One way to get around having to properly set correction equations when performing ID is to use isotope pattern deconvolution (IPD), which not only corrects for spectroscopic interference but also provides the added bonus of correcting for mass bias! For example, the measured count rates of all Se isotopes \((m/z ~76\text{–}78, 80, ~\text{and} ~82)\) after the addition of \(^{77}\text{Se}\) to a sample and those of Br \((m/z ~79\text{ and} ~81)\) were used by IPD to calculate the isotopic composition of Se in the mixture (85). This composition should be a linear function of the natural isotopic composition of Se and the isotopic composition of the \(^{77}\text{Se}\) spike, in the absence of spectroscopic interference and mass bias. Thus, the SOLVER application of Excel can be used to iterate correction factors (for spectroscopic interferences and mass bias) so as to minimize the variance of the multiple-linear regression model (85). Not only are the resulting correction factors in agreement with those found by external correction, but they do not require the measurement of standards with certified isotopic composition. Hence, with IPD, IDA becomes a truly absolute quantification method, as the measurement of a standard is no longer required. Unfortunately, this approach is not applicable to elements, such as Pb, whose isotopic composition varies in nature, as the isotopic composition of the analyte must be known.

During the determination of sulfur by ICP-QMS (or ICP-TOFMS) with a dry plasma, spectroscopic interferences from oxygen contaminants can be problematic in the absence of a C/RC. In one study, the Ar ICP itself was identified as the main source of oxygen, which could be drastically reduced using an argon gas purification system (86).

**Nonspectroscopic Interferences**

The most widely used means of compensating for nonspectroscopic interferences, also called matrix effects, and drift is IS. For the approach to be efficient, the rule of thumb is to select an internal standard that matches analyte properties, especially mass and sometimes first ionization potential (FIP), at least in the case of analytes with high FIP. For example, during the analysis of geologic glasses, the elemental sensitivity ratios (with respect to an internal normalizing element) showed a clear dependence on both mass and FIP (87). However, when performing multielement analysis across the mass range, only a few (if not a single) internal standards can usually be used, as they must not be present in the sample. According to the literature, many people appear to get satisfactory compensation, even when properties of the internal standards do not match those of analytes. (In fact, previous works by this author’s group have shown that even an argon dimer can be used for this purpose in some cases, on instruments that do not suffer from a secondary discharge.) A study was thus conducted by ICP-TOFMS using 51 elements and every possible internal standard/analyte combination between them while varying ICP sampling position, sample uptake rate, NaCl concentration \((0\text{–}500 \text{ mg/L})\), and \(\text{CH}_3\text{COOH}\) concentration \((0\text{–}10\%)\) in an attempt to establish a correlation that would allow a priori selection of an internal standard (88). Of all the chemical and physical properties considered (mass, first IP, second IP, enthalpy, free energy, entropy, electronegativity, ion mobility, and charge in solution), similarity in mass stood out as the most important criterion for a good internal standard, especially to compensate changes in sample delivery rate, but several exceptions were found, such as in the presence of organic component (88). Nonetheless, the good internal standards identified by the Visual Basic program that was written to rank internal standards based on the relative standard deviation (RSD) of the analyte/internal standard signals ratio over the range of conditions (88) also performed satisfactorily on different ICPMS instruments (89).

Because the matrix can affect various processes involved in ICPMS, i.e., aerosol production, aerosol processing in the ICP (which ultimately leads to ion production), ion extraction through the interface, and transmission of a positive ion beam through the mass spectrometer, nonspectroscopic interferences are complex and thus difficult to mitigate. For instance, Coulomb fission during conventional sample introduction, i.e., with a concentric nebulizer and Scott double-pass spray chamber, is a likely explanation for the significant analyte signal enhancement that is sometimes reported. Indeed, the fact that 0.02 M Na enhanced even the signal of analytes that should be completely ionized in the ICP can best by rationalized through an increase in the amount of analyte reaching the plasma as a result of a matrix-induced shift in aerosol droplet size distribution (90). Supporting evidence was obtained through axial profiling of the ICP under otherwise constant operating conditions: a shift in the profile of the oxide fraction (i.e., \(\text{MO}^-/(\text{MO}^+ + \text{M}^+ + \text{M}^{2+})\)) occurred in the presence of 0.02 M nonvolatile ionic matrix (\(\text{NaNO}_3\), \(\text{KNO}_3\), or \(\text{CaNO}_3\)) versus that observed in 1\% v/v \(\text{HNO}_3\), without any apparent change in sample introduction efficiency (90). Furthermore, the shift was linearly correlated to the specific molar volume of the matrix cation, commensurate with the fact that, for a given size of droplets, those containing the larger cations will have less solvent and evaporate sooner. This then increased the likelihood that the Rayleigh limit would be reached, leading to explosion into smaller droplets, which are easier to carry into the plasma and thus increasing analyte transport efficiency, without significant changes in the overall sample introduction efficiency.

The presence or not of a shield around the torch, which is used to mitigate a secondary discharge in the interface of instruments that do not have a load coil configuration that minimizes the potential of the ICP versus the interface, can also affect the level of nonspectroscopic interferences. Indeed, without a shield, Ar ions are predominant and may control space charge effects, making the latter less dependent on sample matrix. With a shield, Ar ions are suppressed to the point where matrix ions
may predominate and then control space charge effects, which then change with sample matrix (91). Exacerbated matrix effects with a shielded torch compared to an unshielded one was reported during continuous nebulization (91) and FI (92). Reoptimization of, for example, the omega-lens of an Agilent ICP-QMS instrument must then be carried out in the presence of the most concentrated matrix, so as to make the measured isotope ratio as similar as possible to that expected from natural abundances (91). Such optimization is especially important for lighter elements, such as Cr, which are most susceptible to space charge effects. The latter can also be reduced using FI, although the alleviation may depend on the matrix element. For example, with an unshielded torch, 5000 mg/L Na or Bi caused around 45% analyte signal loss in continuous nebulization mode but only around 20% in FI mode, whereas 5000 mg/L Ba induced 90% analyte suppression in FI mode (92). Yet, the heaviest matrix element (Bi in this case) would be expected to exert the greatest suppression, irrespective of the sample introduction mode. Clearly, such observations deserve further investigations. As Ba has a greater tendency to form oxides than Bi, perhaps the increased matrix effects with Ba is linked to the oxide formation process?

For instance, when testing different high sensitivity skimmers in dry plasma mode, a large nonlinear mass fractionation component was observed, which was attributed to oxide formation near the skimmer surface (93). In the case of Nd, an isotope dependency not linearly related to mass characterized the extent of oxide formation and mass fractionation; and a decrease in Nd isotope ratio upon changing skimmer geometry was accompanied by an increase in the corresponding NdO isotope ratio, consistent with mass balance (93). Addition of nitrogen to the aerosol carrier gas decreased mass fractionation along with oxide formation, the NdO\(^+\)/Nd\(^+\) ratio becoming <0.001 with only 0.15% N\(_2\) (93). In any case, the deviations between the measured Nd isotope ratios and the expected values correlated those in nuclear charge radii from a linear function of mass, providing, for the first time, evidence of nuclear volume effects on instrumental mass fractionation in ICPMS (93)!

However, operating conditions, including the sample introduction system (i.e., wet vs dry aerosol), can exert a significant effect on mass bias. In fact, a change in plasma gas temperature, which affects the kinetic energy distribution of the ions and, in turn, their transmission through the ion optic, may result in a systematic positive bias toward heavier isotope ratios because lighter isotopes are more easily lost through diffusion in the ICP, collisions in the interface, or space charge effects (94). Optimization of the operating conditions to maximize the sensitivity of a given isotope exacerbates this discrimination, to the point where even simultaneous detection by MC-ICPMS cannot compensate for it (94). On the other hand, operating under cooler plasma conditions with a wet aerosol may mitigate this effect during the measurement of isotope ratios. For example, at high carrier gas flow rate and without retuning the ion optics for maximum sensitivity, which resulted in a 40% sacrifice in sensitivity, the nonspectroscopic interference induced on \(^{146}\text{Nd}^{+}/^{144}\text{Nd}^{+}\) by 10 \(\mu g/g\) Ho decreased 6-fold compared to that observed under maximum sensitivity conditions (94). This approach is, however, not as effective when the solvent load is reduced, such as when the sample uptake rate is lowered or a desolvation system is used.

Because finding operating conditions minimizing nonspectroscopic interferences can be time-consuming, even more so when samples of widely varying matrices have to be analyzed, chemical separation of the analyte from the matrix is often carried out. However, if highly precise isotope ratios are desired, such as for Pb isotope ratios application in mantle geochemistry, then even residual matrix components may be problematic. For example, the enhancement of Pb and Tl sensitivity caused by Ca, Mg, Al, or Fe increased as the molar ratio of matrix/analyte increased up to 50 but then leveled off for greater molar ratios (95). Interestingly, Ar\(^+\)/Ar\(^{2+}\) concurrently increased and reached a plateau at the same molar ratio of 50, suggesting that the matrix reduced the Ar charge density, which in turn allowed a greater proportion of analyte to stay in the core ion beam (95). In any case, because of this leveling off, addition of a common matrix to samples and standards essentially eliminated the effect caused by residual matrix (95). This simple approach should thus be seriously considered instead of investing more time and energy in completely separating the analyte from the matrix. In fact, even resin-derived contaminants introduced during the process of separating the analyte from the matrix can be a significant source of matrix effects, leading to inaccurate measurements, especially when looking at small natural variations in isotopic compositions, such as those of Cd and Zn in the environment (96).

**ISOTOPE RATIOS**

**Reviews.** A nice tutorial review was written on the determination of isotope ratio by single-collector and MC-ICPMS (97). It discusses the capabilities of the different types of instruments available, ways of correcting for the biases arising from mass discrimination and detector dead time, and examples of both accepted and exotic applications (97). The application of ICPMS and LA-ICPMS to the measurement of isotope ratios in biological materials and single particles was also reviewed (98). Examples include tracer experiments and ID techniques combined with nanoFI for the analysis of very small biological samples volumes; the analysis of protein bands in gels by LA-ICPMS following gel electrophoresis; and imaging thin slices of brains or even single particles with LA-ICPMS (98). The use of enriched stable isotopes as tracers in living organisms is rapidly broadening, thanks to the high sensitivity of ICPMS and to the availability of different strategies to either cope with spectroscopic interferences, such as C/RC and DRC technologies, or facilitate the measurement of isotope ratios, such as MC-ICPMS (99). Another expanding area is quantitative protein analysis by ICPMS with sulfur ID, where the compound-independent ionization feature of ICPMS enables species-unspecific ID, i.e., one isotopically enriched sulfur spike is sufficient to quantify completely separated (by chromatography or electrophoresis) peptides or proteins whose identities are known (100). For the determination of the phosphorylation degree of a protein, measurements of the P/S ratio can be performed, while the stoichiometry of a metalloprotein can be determined from the metal/S ratio (100). The determination of proteins can be facilitated by derivatizing them with metal tags, which are then detected with greater sensitivity (100).

**Original Approaches.** Pb, Sm, and Ni isotope ratio precisions of less than 0.003% RSD could be obtained in most cases (as opposed to 0.07% to 0.15% RSD without correction) by MC-ICPMS.
in clean acidified solutions using Tl, Eu, and Cu as internal standards, respectively (65). The internal standard measurements were used to apply a linear isotope ratio mass bias correction to all samples and standards, and following mass bias correction, analyte ratios were corrected for time-dependent isotope ratio drift. Any proportional error arising from the assigned isotope ratios of the internal standard was then compensated using the average of the mass- and drift-corrected analyte isotope ratios of the calibration standard (65).

Fluctuations in the density of the ion beam are a significant source of imprecision during the measurement of the isotope ratio by sequential type mass spectrometers. Decreasing the dwell time so as to make the measurements as close to simultaneously as possible can reduce this effect. Using a pressurized C/RC can also alleviate this effect, as it temporally homogenizes the ion beam by reducing the kinetic energy of ions through collisions, which increases their residence time, thereby allowing different ion packets to overlap. Hence, using a C/RC, it is possible to both resolve a spectroscopic interference from a polyatomic ion and achieve an isotope ratio precision that is close to counting statistics. This was demonstrated for the measurement of the $^{44}\text{Ca}/^{40}\text{Ca}$ isotope ratio using a DRC with NH₃ reaction gas and internal correction for mass bias using $^{43}\text{Ca}/^{48}\text{Ca}$, which achieved precisions close to those obtained by MC-ICPMS, following optimization of DRC and ICP operating conditions (101). For example, the nebulizer gas flow rate is an important parameter to optimize, the most precise isotope ratio not being necessarily observed at the flow rate corresponding to maximum sensitivity. Indeed, increasing the nebulizer gas flow rate decreases the temperature in the central channel of the ICP, which changes the densities of Ar⁺ and analyte ions while reducing their mean kinetic energy. This, in turn, results in a mass-dependent redistribution of ion densities and thus differing extraction efficiencies for ions of different $m/z$. Conversely, increasing rf power reduces mass discrimination but is not desirable in this case because it would increase the formation of Ar⁺ ions that interfere with Ca (101).

Compared to ICP-SFMS, ICP-QMS with C/RC provides better isotope ratio precision in the case of elements (such as Se) suffering from spectroscopic interference (82). No flat-top mass spectral peaks, which provide high isotope ratio precision in low resolution, can be obtained with increased mass resolution in ICP-SFMS. Ar-containing spectroscopic interferences are better alleviated with a He/H₂-pressurized C/RC than by increasing mass resolution. The sensitivity is higher with ICP-QMS and a C/RC than with ICP-SFMS at increased mass resolution, which improves counting statistics. Hence, despite the increased mass bias observed with a He/H₂-pressurized C/RC, as a result of the collisions occurring in the cell, better Se isotope ratio precision and detection limits are nonetheless achieved (82).

Analog detection is preferred over the pulse counting mode to eliminate one source of error that degrades the precision of isotope ratio: the dead time of the detector, when ions arrive too fast to be counted by the detector at high analyte signal. However, with some TOFMS instruments, a systematic bias in isotope ratio measurements can be observed, which depends on the value of the isotope ratio, the analyte concentration, and the gain of the electron multiplier tube detector (102). This problem arises because of the threshold voltage that must be used to filter out noise and which translates into more attenuation of weak signals than large ones. As a result, the apparent detection efficiency varies, which causes an increasing systematic error as the isotope ratio departs from unity. This effect can be reduced by increasing the gain of the detector, albeit at the cost of reduced detector lifetime. Alternatively, a detector efficiency correction can be made. With the use of solutions generating known isotopic ratios, correction factors are calculated as a function of signal and a third order polynomial is fitted to these data, which is then applied to correct measured ratios (93). However, as the shape of the correction curve varies between elements, a correction curve must be established for each element being determined. The best precision is obtained with both methods (i.e., increased gain and efficiency correction) (102).

The isotope ratio precision achievable with MC-ICPMS combined with the straightforward introduction of solutions makes it rival isotope ratio mass spectrometry, as no combustion of carbon into CO₂ or derivatization is required prior to analysis and, hence, no correction for oxygen is required, which greatly simplifies each analysis (58). Internal mass bias correction of the $^{13}\text{C}/^{12}\text{C}$ isotope ratio using $^{11}\text{B}/^{10}\text{B}$ results in corrected carbon isotope ratios with typical combined relative uncertainties <0.05%, which is sufficient for food authenticity and pharmaceutical counterfeit detection studies in addition to allowing the measurement of SI traceable carbon isotope amount ratios (58). Regarding uncertainties, unless the isotope ratio is treated as a single pseudovariable with its experimental uncertainty, care has to be taken when propagating the uncertainties of the individual ion signals from which a ratio is computed. Indeed, a simple summation of the relative variances is inappropriate, as it is valid only for independent variables, which is certainly not the case for two analyte ions that are measured simultaneously with MC-ICPMS or ICP-TOFMS (103). Such an approach overestimates the uncertainty, which must be reduced by a term depending on the extent of correlation between the two signals (103).

In the case of the isotope ratios of some radioisotopes (such as $^{133}\text{Cs}$, $^{134}\text{Cs}$, $^{135}\text{Cs}$, and $^{137}\text{Cs}$) in spent nuclear fuels, for which there is no pair of stable isotopes (as Cs is monoisotopic) available for internal correction of mass bias, an external correction must then be carried out through sample-standard bracketing and mass bias interpolation using elements (Eu and Sb) that are close in mass to the analyte, in addition to a two-step separation of the analyte from the matrix prior to the analysis to eliminate sources of spectroscopic interference (104). Another example is Pb, for which isotope ratio measurements can be reliably carried out by MC-ICPMS down to 0.05 ppm levels but not below this because of short-term fluctuations in mass discrimination (105). Although the most efficient way of correcting such fluctuations would be internally, with a constant isotope ratio of the same element, because this is not possible for Pb, which does not possess a stable isotope pair, the next best alternative must be used, i.e., adding a TI internal standard (105). Furthermore, when nonspectroscopic interferences induce large mass bias effects, separation of the
analyte from the matrix is often a necessity for accurate and high-precision isotope ratio measurements.

When a spectroscopic interference is present, which cannot be completely eliminated by sample pretreatment, applying a sectional power law correction, where different power laws are used based on the analyte/interfering agent ratio (such as $^{170}$Lu/$^{170}$Yb ratios between 2 and 40, between 40 and 130, and greater than 130), can provide accurate and precise isotope ratio measurements, such as of $^{170}$Lu/$^{170}$Yb ratios in geological materials (106). Because the accuracy and precision of isotope ratios depends on the absolute amount of analyte ions reaching the detector, a sample introduction system providing a higher sample introduction efficiency in the plasma and the use of high sensitivity sampling cone can significantly improve the quality of the results at low analyte concentrations (1 ng/g) (107).

**Isotope Dilution.** Isotope dilution, which is the calibration strategy providing the most accurate and precise results, requires two isotopes free of spectroscopic interference per analyte, equilibration of the isotope spike with the sample, and correction of the analyte isotope ratio for mass bias. Another critical step is blank subtraction, which can degrade the accuracy of ID results if not performed correctly. Although direct subtraction of a procedural blank is often done, care should be taken to only perform it when the blank contributes only to the primary ID process. When it contributes to both the primary and reverse ID processes, such as when performing online SPE, only a fraction of the blank concentration should be subtracted from that of the sample (38).

### HYPHENATION TO SPECIATION METHODS

**Reviews.** Because the toxicity, bioavailability, and mobility of an element depend on its chemical form, determination of its total concentration provides little if any information on, for example, the safety of a food item. As a result, numerous speciation analysis methods were and continue to be developed for a variety of sample types and were the subject of a review article (108). Critical reviews were also written on speciation analysis methods aimed at specific elements: Sb in biological matrices (109), Se in nutritional and food products (110), and $^{129}$I in environmental and biological samples (111). While ID allows species quantification, the complementary use of molecular MS (and MS/MS) using electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI) is often required for species identification and structural characterization (110). Although calibration using ID is renowned to provide results with unrivalled accuracy and precision in elemental speciation analysis, a number of fundamental prerequisites must be fulfilled, which were critically reviewed in terms of their effect on accuracy and of the practical limits of their validity (112). Anyone performing speciation analysis should read this article, as it provides valuable information on how to obtain the best results using this powerful calibration strategy.

**Nonchromatographic Methods.** While chromatographic separation techniques coupled to ICPMS are often used for speciation analysis, they take time and, as a result, are not widely used on a routine basis. Furthermore, full speciation analysis is often not required for risk assessment, such as when only some species are toxic. For example, Cr(VI) is toxic not Cr(III). A separation method that is specific to Cr(VI) would be less time-consuming and thus more cost-effective. Such methods are also more widely available, as they do not require chromatographic equipment, and often provide competitive detection limits (113). That is why nonchromatographic methods available for the speciation analysis of clinical, environmental, and food samples were reviewed (113). Some other examples are included in Table 1.

**Liquid Chromatography.** Because of the robustness, reproducibility, and gradient separation capabilities of liquid chromatography (LC), in addition to its applicability to a wide variety of compounds, irrespective of their volatility and thermal stability, LC is the most widely applied separation technique. However, with the use of ICPMS detection, identification of species can only be made based on retention times, through comparison with standards. At least two different separations are then required to confirm the absence of coeluting analyte species (128). When standards are not available, identification must be done using ESI-MS/MS, which also provides structural information and is thus essential when studying the metabolism of specific compounds (128). On the other hand, ICPMS complements ESIMS/MS as it, for instance, allows the absolute quantification of proteins (bovine serum albumin, superoxide, and metallothionein-II dismutase) via sulfur monitoring, if oxygen is used in a C/RC to form SO\(^+\), thereby eliminating the O\(_2\)^+ interferences on S (129). Proteins separated by size exclusion chromatography can be quantified by postcolumn ID with $^{35}$S, $^{65}$Cu, and $^{65}$Zn, the latter two providing the S/Cu and S/Zn ratios in proteins.

However, only limited organic solvent load can be directly handled by an Ar ICP whereas a high organic solvent content often improves the separation in conventional LC. One way around this dilemma is to use capillary LC, which operates at 8 µL/min and couple it to a micronebulization system, such as a high-efficiency nebulizer coupled to a single-pass mini-chamber, as this then minimizes the total solvent load in the ICP without imposing any constraint on the chromatography (130). As subtle differences in nebulizer and spray chamber designs can translate into large differences in sensitivity as well as in dead volume, which increases the chromatographic peak width, explicit evaluation of different sample introduction systems should be carried out to select the best one (130). To further minimize sample loading into the ICP, nanoLC can be used in combination with a nanonebulization system (131). This approach was useful along with nanoLC–ESI-MS for the characterization of Se-containing proteins in Se-rich yeast, following two-dimensional gel electrophoretic separation of the proteins, identification of the relevant Se-containing spots by LA-ICPMS, and in-gel tryptic digestion (131).

The practical problems and limitations of multiple hyphenation of liquid chromatography to different detectors, such as LC–ICPMS–TOFMS, were reviewed (132). The biggest deterrents are the capital cost and the implications in terms of the huge amount of data generated by such systems. One way to partly get around these problems is to design a single mass spectrometer that can handle two different ionization sources. This is possible with TOFMS and preliminary work in this direction was done where both an ICP and ESI sources were installed orthogonally on the same TOFMS instrument (133). Each source has its own first
<table>
<thead>
<tr>
<th>analyte species</th>
<th>sample matrix</th>
<th>sample pretreatment</th>
<th>separation method</th>
<th>ICPMS</th>
<th>calibration strategy</th>
<th>comments</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>SeO$_3^{2-}$, Se-methionine</td>
<td>rat urine</td>
<td>filtration; dilution 1:1</td>
<td>LC on C$_{18}$; 1 mL/min pH 4.5 100 mM NH$_4$Ac/5% MeOH</td>
<td>QMS with C/RC; 4 mL/min H$_2$</td>
<td>postcolumn ID with $^{32}$Se standard</td>
<td>IPD discriminates endogenous and supplemented Se; species identification with ESI-Q-TOF</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\mu$-affinity LC on heparin-sepharose, blue-sepharose (latter bypassed for some species); 0.3 mL/min pH 7 AcNH$_3$, 0.05–1.5 M capillary GC; 2 mL/min He; 1 $\mu$L injection; splitless</td>
<td>SFMS with APEX high-efficiency sample introduction</td>
<td>EC with SeCys standards or ID with postcolumn $^{77}$Se addition</td>
<td>miniaturized separation in $\leq$ 7 min; biased EC results when $R = 10,000$ but not when $R = 4,000$</td>
<td>64</td>
</tr>
<tr>
<td>dimethyl-selenide, dimethyl-diselenide</td>
<td>garlic, onion and their juice</td>
<td>solid mashed; mixed with water and sonicated; NaCl and stirring bar added; headspace sampling with sorptive bar; ultrasonic desorption with MeOH</td>
<td>photochemical VG in quartz coil (around water-cooled UV lamp) with organic acid pH adjusted to 4.9 with CH$_3$CO$_2$Na; SPE; elution with 2 M HNO$_3$</td>
<td>QMS</td>
<td>EC</td>
<td>holding a sorptive bar above the sample solution allowing sampling of volatile organoSe species, irrespectively of the complexity of the sample matrix gas/liquid separation eliminates Cl-containing interferences alizarin used to bind Cr(III) and prevent its oxidation to Cr(VI)</td>
<td>115</td>
</tr>
<tr>
<td>Se(IV)</td>
<td>table salt, mineral, and waste waters cow's milk</td>
<td>salt samples diluted in high-purity water</td>
<td>photochemical VG in quartz coil (around water-cooled UV lamp) with organic acid pH adjusted to 4.9 with CH$_3$CO$_2$Na; SPE; elution with 2 M HNO$_3$</td>
<td>QMS with DRC; 0.85 mL/min O$_2$ reaction gas</td>
<td>EC</td>
<td>alizarin used to bind Cr(III) and prevent its oxidation to Cr(VI)</td>
<td>116</td>
</tr>
<tr>
<td>Cr(VI)</td>
<td>cow's milk</td>
<td>mixed with pH 3.5 buffer, sonicated and centrifuged; supernatant mixed with 0.001% alizarin</td>
<td>photochemical VG in quartz coil (around water-cooled UV lamp) with organic acid pH adjusted to 4.9 with CH$_3$CO$_2$Na; SPE; elution with 2 M HNO$_3$</td>
<td>QMS</td>
<td>EC</td>
<td>alizarin used to bind Cr(III) and prevent its oxidation to Cr(VI)</td>
<td>117</td>
</tr>
<tr>
<td>7 As species</td>
<td>seafood</td>
<td>artificial saliva leachates diluted 1:5 prior to injection on IEC column</td>
<td>IEC on AS-7; 1.35 mL/min 1% MeOH/0.5–50 mM HNO$_3$</td>
<td>QMS</td>
<td>EC</td>
<td>7 bioaccessible As species were separated within 18 min</td>
<td>118</td>
</tr>
<tr>
<td>6 As species</td>
<td>seafood</td>
<td>0.25 g mixed with 1.75 g of diatomaceous earth; transferred into syringe containing 2 g of C$_{18}$; elution of As species with 50% MeOH; evaporation of MeOH</td>
<td>IEC on AS-7; 1.35 mL/min 1% MeOH/1–80 mM HNO$_3$</td>
<td>QMS</td>
<td>EC with standard As compounds in saliva</td>
<td>7 bioaccessible As species were separated within 18 min</td>
<td>119</td>
</tr>
<tr>
<td>5 As species</td>
<td>urine, rabbit serum, microdialysates</td>
<td>0.5–1 g sample mixed with 0.5–1 g of isotope spike solution</td>
<td>IEC-UV/TiO$_2$-hydride generation; 1 mL/min 20 mM phosphate buffer pH 6.0</td>
<td>QMS</td>
<td>EC (using peak area)</td>
<td>IEC effluent flow is segmented with Ar to avoid peak broadening during photooxidation (catalyzed by TiO$_2$) solvent containing As$\rightarrow$APDC complex directly injected in furnace</td>
<td>120</td>
</tr>
<tr>
<td>As(III)</td>
<td>waters</td>
<td>add NH$_4$Ac, APDC and adjust pH to 3; add &quot;solvent bar&quot; and stir</td>
<td>&quot;solvent bar&quot; microextraction</td>
<td>QMS with ETV</td>
<td>EC</td>
<td>IS corrected for changes in injection volume and in ICPMS sensitivity between separations detection limit limited by essentially constant background signal at m/z 32</td>
<td>121</td>
</tr>
<tr>
<td>carboplatin</td>
<td>plasma</td>
<td>mixed with citrate and sodium diatrizoate IS</td>
<td>CE; 10 mM phosphate buffer (pH 7.4); 30 kV for 4 or 10 min</td>
<td>QMS with 2 commercially available interfaces</td>
<td>EC through makeup liquid with IS in sample</td>
<td>IS corrected for changes in injection volume and in ICPMS sensitivity between separations detection limit limited by essentially constant background signal at m/z 32</td>
<td>122</td>
</tr>
<tr>
<td>sulfur species</td>
<td>gasoline, diesel fuel, heating oil</td>
<td>0.5–1 g sample mixed with 0.5–1 g of isotope spike solution</td>
<td>capillary GC; 1.6 mL/min Hc; 3:1 to 50:1 split injection ratio, depending on S concentration</td>
<td>QMS with in-house heated transfer line</td>
<td>species-specific ID (with $^{34}$S-labeled species)</td>
<td>IS corrected for changes in injection volume and in ICPMS sensitivity between separations detection limit limited by essentially constant background signal at m/z 32</td>
<td>123</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Analyte species</th>
<th>Sample matrix</th>
<th>Sample pretreatment</th>
<th>Separation method</th>
<th>ICPMS</th>
<th>Calibration strategy</th>
<th>Comments</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfur species</td>
<td>Vacuum gas oil, gasoline, diesel fuel, naphtha, heating oil</td>
<td>1 g of sample mixed with 1 g of IS (2-ethyl thiophene or dibenzothiophene) in hexane</td>
<td>Capillary GC; 1.6 mL/min He; 1 µL injection; split ratio 3:1 to 5:1 split ratio, depending on S concentration</td>
<td>QMS with in-house heated transfer line</td>
<td>IS and postcolumn ID with 34S-labeled dimethyl-disulfide</td>
<td>Purification of Ar gas substantially reduced O2 background; accuracy independent of coeluting hydrocarbons</td>
<td>86</td>
</tr>
<tr>
<td>MeHg</td>
<td>Human hair, tuna fish</td>
<td>3 h digestion at room temp with 25% TMAH for tuna; 2 h digestion at 70 °C with 6 N HNO3 for hair; derivatization with NaBEt4, and extraction into hexane with NaDDTC into n-hexane; butylation</td>
<td>Capillary GC; 25 mL/min He; 11 L/min Ar nebulizer gas; 2 µL injection; splitless</td>
<td>MC-ICPMS; double-inlet injector for transfer line</td>
<td>Species-specific ID with 199Hg-enriched MeHg</td>
<td>No loss of species-specific information does not lead to loss of species-specific information</td>
<td>124</td>
</tr>
<tr>
<td>Pb and Hg species</td>
<td>Tuna, codfish, solen meat</td>
<td>Hydride generation with pH gradient from 7 to 1 during continuous NaBH4 addition; hydrides collected in cryogenic trap</td>
<td>Low-temperature GC with temperature gradient</td>
<td>QMS with in-house heated transfer line</td>
<td>EC with PrPCl3 IS</td>
<td>Nebulizer mass flow could be applied to the determination of the conditional stability constants of metal complexes using only a guard column (134). The conditional stability constants that were obtained from a linear regression of the logarithm of the ratio of the peak area of the metal complex to that of the chelation number as the intercept and as the slope. (128) This extraction can be combined to a cleanup step if the solid mixture is loaded into a syringe containing a high phase volume, allowing the analyte to be easily extracted at room temperature, and atmosphere pressure with a mild reagent (129). This extraction can be combined to analyze the original sample matrix for analyte loss.</td>
<td>125</td>
</tr>
<tr>
<td>As, Sn, Sb, Hg species</td>
<td>Sediment, compost, soil</td>
<td>Continuous cold VG using SnCl2</td>
<td>LC-hydride generation; C16 0.3 mL/min mobile phase with 70% MeOH</td>
<td>QMS</td>
<td>ID with inorganic 199Hg</td>
<td>No loss of species-specific information</td>
<td>126</td>
</tr>
<tr>
<td>Inorganic Hg</td>
<td>Seafood</td>
<td>Dissolution in TMAH at room temperature; filtration through 0.4 µm membrane filter</td>
<td>Continuous cold VG using SnCl2</td>
<td>QMS</td>
<td>EC (using peak height)</td>
<td>No loss of species-specific information</td>
<td>53</td>
</tr>
<tr>
<td>Methylthins</td>
<td>Seawater</td>
<td>Extraction into hexane</td>
<td>Continuous cold VG using SnCl2</td>
<td>QMS</td>
<td>EC (using peak height)</td>
<td>No loss of species-specific information</td>
<td>127</td>
</tr>
</tbody>
</table>

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where the transfer line ends in the ICP torch (1.8 cm behind the load coil) is critical in terms of sensitivity and chromatographic peak width (86, 123). Species-specific ID, where the sample is spiked with an isotope-labeled species that is chemically identical to the analyte, provides the most accurate results because it compensates for partial analyte loss during sample preparation and there is no need to measure the recovery of the separation step (123). However, an individual spike is required for each species, which is time-consuming for the determination of multiple species, not to mention that each isotope-labeled species must be synthesized, which is not practical for routine speciation analysis. Species-unspecific ID, where a single isotope spike is added following species separation, is easier to implement, but it does not compensate for analyte loss during sample preparation and separation. Nonetheless, it readily provides accurate results with methods achieving quantitative recoveries. Although post-column ID is easily implemented with LC, a special dosing unit is required to perform a continuous addition of a constant amount of spike to the GC effluent. One way is to use an Ar gas cylinder to which an isotope-labeled compound was added, provided the compound was thoroughly mixed and allowed to equilibrate for a couple of hours before postcolumn spiking is done using an electronic flow controller (86). Spiking the sample with a S internal standard with natural isotopic composition prior to injection compensates for uncertainties in the injected volume in addition to allowing isotope spike mass flow calibration (86). Complementary structural characterization of the species usually requires electron ionization MS (EI-MS) or EI/MS/MS (86).

Coupling GC to MC-ICPMS enables species-specific isotope ratio measurements, such as those of different Hg species (124). With the use of an isothermal temperature program, the chromatographic peak width of the eluted species was significantly broadened, which facilitated the measurement of isotope ratios, the best precision being obtained by integrating all signals above 5% of the peak height (whereas that obtained from point-by-point isotope ratios was inadequate) (124). For low analyte levels, counting statistics were improved by preconcentrating the derivatized samples under a gentle stream of Ar so that the concentration of Hg became 200–250 ng/g (124). For mass bias correction, standard–sample–standard bracketing was performed and a Ti solution was nebulized, with the wet aerosol being merged with the GC effluent in a dual-inlet torch (124). The presence of water also made the plasma more robust and less susceptible to the disturbance caused by the solvent peak (124). With an external 2 standard deviation precision of 0.56 ‰ for δ²⁰⁹Hg, the approach could detect both mass-dependent and mass-independent fractionation in environmental samples, such as the mass-independent fractionation of ¹⁹⁹Hg and ²⁰¹Hg in tuna fish (124).

As can be seen in Table 1, several groups prefer a wet ICP for speciation analysis with GC separation, as it not only increases plasma robustness but it also facilitates the introduction of internal standards. In combination with a suitable sample preparation, such as butylation (125) or hydride generation with a pH gradient during mixing with NaBH₄ (126), multielement speciation analysis becomes possible, which takes full advantage of the multielement detection capability of ICPMS.

**Capillary Electrophoresis.** A review focused on Se speciation analysis by CE, including the separation conditions required for various applications as well as interfaces to ICPMS (135). Interfacing CE to ICPMS is indeed not as straightforward as LC because a potential must be maintained across the CE capillary to achieve a separation, which must not be degraded by suction from the nebulizer. A micronebulizer is normally used, which still requires a makeup flow to maintain continuous nebulization without degrading the CE separation (136). This makeup flow can simultaneously serve for the introduction of an internal standard (136). Nonetheless, of all the hyphenated techniques that can be used to study the interactions between metals or metalloids and biomolecules, which is extremely useful in biology, medicine, pharmacy, environmental sciences, nutrition, etc., CE provides a rapid separation with high resolution as well as minimal sample and reagent consumption while not significantly disturbing the equilibrium existing between metals and biomolecules in the sample (137). It is increasingly used to study interactions between metals and metalloids with natural ligands, such as humic and fulvic acids, as well as with metalloproteins (137). For example, it is important to study the complexation behavior of actinides with humic acid for the design and long-term risk assessment of radioactive waste repository (136).

Although some interfaces are commercially available for coupling CE to ICPMS, the use of CE–ICPMS remains limited compared to other separation strategies because its operation requires experience (122). The different interfaces may provide similar performance in terms of peak shape and width as well as repeatability of migration times, but one may be easier to optimize and hence may thus result in better precision and sensitivity for a given application (122). With dependence on the application, the introduction of an internal standard through the makeup flow may not be sufficient to compensate for changes in sensitivity, as a result of solid deposition on the cones for instance, and in any case, would not correct for changes in injection volume. The addition of an internal standard to the sample will correct for both, as long as it does not interact with the analyte (122).

To avoid having to optimize the interface between CE and ICPMS and hence eliminate any pressure-induced flow from a nebulization system, droplets of the CE effluent can be collected onto a poly(ethylene terephthalate) glycol sample plate placed on an x–y stage in a subatmospheric deposition chamber (138). A liquid junction is used to connect the CE capillary to a deposition capillary, flow being induced in the latter by the reduced pressure in the chamber (138). Substrate-assisted laser desorption is then used to vaporize each fraction into ICPMS. Although this approach preserves the high separation efficiency of CE, allowing the high-resolution separation of Cr(III) and Cr(VI) within 25 min (138), its accuracy has yet to be demonstrated through the analysis of real samples.

**HYPHENATION TO VAPOR GENERATION**

Chemical vapor generation, where the analyte reacts with a chemical reagent to form a volatile or semivolatile analyte species, is often used to separate the analytes from troublesome sample matrices, increase selectivity, or increase sensitivity through the higher sample introduction efficiency that can be achieved compared to conventional sample introduction with a nebulizer and spray chamber. Vapor generation (VG) can also be achieved
using ultraviolet (UV) irradiation of solutions containing acetic acid, an approach that was used to enhance ICPMS sensitivity for iodine, an element whose degree of ionization is estimated to be about 20% in the ICP (139). A 50 mL water-jacketed cyclonic spray chamber was modified so as to fit a 6 W Hg pen lamp in its center, which, although it provided only about 3 s of UV irradiation, still resulted in a 40-fold increase in sensitivity (139). An alternative system that provided similar performance but did not require modifying a spray chamber involved wrapping 1 m of polytetrafluoroethylene tubing around a 15 W Hg lamp and connecting this tubing to the inlet of a conventional nebulizer/spray chamber system (139). However, both approaches were blank-limited by the acetic acid required for photochemical VG. A third approach involved a 100 mL double-pass spray chamber placed between a 17.4 W UV grid lamp and a coated mirror to reflect UV radiation back through the spray chamber. Although it provided the highest surface area and longest residence time for UV irradiation and gas/liquid separation, the lowest response was nonetheless obtained, along with long washout times and signal fluctuations (139). The best organic acid for a given application depends on the composition of the sample solution being analyzed, including the reagents used for dissolution (56, 116). In any case, photochemical VG is greener than chemical VG, as both the reagents and byproduct are more environmentally friendly; furthermore, less hydrogen gas is generated, causing negligible disturbance of the plasma (116).

Whether chemical or photochemical, VG can be invaluable for the measurement of high-precision isotope ratio. Indeed, it inherently separates the analyte from the sample matrix and increases sensitivity compared to conventional nebulization because essentially 100% sample introduction efficiency can be achieved without overloading the plasma, which, because of counting statistics, translates into more precise isotope ratios. This was demonstrated for precise Se isotope ratio measurement with MC-ICPMS using hydride generation, which improved the signal-to-noise ratio by 2 orders of magnitude compared to what can be achieved with conventional nebulization (140). In fact, the isotope ratio precision was then comparable to that obtained with thermal ionization MS without requiring extensive sample pretreatment.

Preconcentration can also be achieved by accumulating the vapor in a trap, which is later released into the ICP. For example, a gold trap can be used to accumulate Hg stable isotopes released by cold VG. However, the sudden release of the vapor into the plasma may result in imprecise ratios because heavy isotopes may be released faster than light isotopes (ref 141 and references therein). To get around this problem, a cold vapor syringe injection interface was developed, where the cold vapor is released into a large-volume gastight syringe, which is then used to introduce the vapor at a constant rate into the ICP (141). Hence, a steady-state signal is generated, which could be corrected for mass bias using Tl (that is continuously introduced with nebulization/desorvation system) along with standard-sample bracketing (141). However, care must be taken to exclude air from the system, as air can perturb the plasma and substantially decrease sensitivity (141). Some examples of quantitative applications of vapor generation for sample introduction in ICPMS are summarized in Table 2.

**Table 2. Selected VG Quantification Methods**

<table>
<thead>
<tr>
<th>analytes</th>
<th>sample matrix</th>
<th>vaporization method</th>
<th>instrument</th>
<th>calibration strategy</th>
<th>comments</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hg</td>
<td>seafood</td>
<td>continuous</td>
<td>QMS</td>
<td>ID with inorganic</td>
<td>GC separation of hydrides would allow speciation analysis, as MeHg forms a distinct hydride than inorganic Hg</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>dissolved in</td>
<td>cold VG using NaBH₄</td>
<td></td>
<td>¹⁹⁹Hg</td>
<td>simple sample preparation with microwave induced combustion</td>
<td>55</td>
</tr>
<tr>
<td>As</td>
<td>seafood</td>
<td>FI hydride</td>
<td>QMS</td>
<td>EC</td>
<td>no plasma instability, as little H₂ is produced by photochemical VG with organic acid</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>dissolved in</td>
<td>generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>nitrile acid</td>
<td></td>
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<tr>
<td>Se</td>
<td>table salt,</td>
<td>photochemical VG</td>
<td>QMS</td>
<td>EC</td>
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<tr>
<td></td>
<td>mineral water,</td>
<td>in quartz coil</td>
<td></td>
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<tr>
<td></td>
<td>wastewater</td>
<td>(around UV lamp)</td>
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<tr>
<td></td>
<td></td>
<td>coated with nano-TiO₂</td>
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<td></td>
<td></td>
<td>and placed in</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>boiling water bath</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>citrus leaves,</td>
<td>photochemical VG</td>
<td>QMS with</td>
<td>EC with standard</td>
<td>both as receiving</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>sois, oysters,</td>
<td>in water-jacketed</td>
<td>DRC</td>
<td>in 5% CH₃COOH</td>
<td>solution during</td>
<td></td>
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<tr>
<td></td>
<td>milk powder</td>
<td>cyclonic spray</td>
<td>(1.4 mL/min O₂)</td>
<td></td>
<td>combustion and as</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>chamber containing</td>
<td></td>
<td></td>
<td>reagent for</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hg pen lamp</td>
<td></td>
<td></td>
<td>photochemical VG</td>
<td></td>
</tr>
</tbody>
</table>

**HYPHENATION TO LASER ABLATION**

**Reviews.** The coupling of LA to ICPMS gives a powerful technique for the direct analysis of solid samples, which has distinctive advantages over glow discharge MS (GDMS) and secondary ion MS (SIMS). Unlike GDMS, it allows lateral profiling and it does not require the high vacuum of SIMS to perform depth profiling, albeit with less depth resolution (i.e., submicrometer vs a few nanometers with SIMS) (142). The important experimental parameters controlling the ablation and LA processes were reviewed and guidelines proposed to avoid fractionation and achieve optimum ablation and particle production (143). Despite these guidelines, a number of experiments are still needed to better understand the technique, which would, in turn, lead to an improvement of LA-ICPMS (143). An example of one area where LA-ICPMS is invaluable is cultural heritage research where quantitative elemental compositional data on an artifact is required through direct nondestructive analysis of the object (144). Hence, LA-ICPMS plays a key role in providing data to, for instance, answer questions on the date, provenance, and use of ancient artifacts, such as pottery, glass, metal objects, written documents, etc (144). The direct measurement of isotope ratios in solids is also enabled by LA-ICPMS, the most precise and accurate ratios being obtained by LA-MC-ICPMS. Nonetheless, the accuracy and precision are limited by instrumental mass bias, isotopic/elemental...
fractionation, and spectroscopic interferences, as was demonstrated by a review of Sr isotope ratios obtained during a decade, which concluded that there was still room for improvement in the correction of spectroscopic interferences (145).

Femtosecond LA-ICPMS is emerging as the preferred direct solid analysis technique because the use of ultrashort (<1 ps) laser pulses reduces nonstoichiometric effects, i.e., elemental fractionation, thereby facilitating the direct determination and depth-profiling of major and trace elements in biological, geological, and other materials, along with the measurement of isotopic ratios (146). This improvement stems from differences in the LA mechanism upon using <1 ps laser pulses instead of >1 ps ones, which were reviewed (146).

**Femtosecond Lasers.** With a low-energy laser (such as an infrared laser), a narrow laser beam must be used to ensure a fluence that is above the ablation threshold. Although this may be fine for microanalysis, it provides low sensitivity as a result of the small ablated volume. To increase sensitivity, the sample removal rate and ablated volume can be increased using, respectively, a high repetition rate laser and a galvanometric scanning beam device, which allows fast movement, at up to 280 mm/s, of the laser beam on the sample surface, with a repositioning precision of ±1 µm (147, 148). A well-defined crater is then created by ablating the sample while moving the 17 µm laser spot along concentric circles trajectories (147).

A similar approach can be used for in-cell ID where, with appropriate carrier gas flow rate, sample translation speed, etc., the high repetition rate laser quickly moves between pellets of a sample and of an isotope-enriched solid so as to achieve their quasi-simultaneous ablation, thereby performing ID spiking during LA (146, 149). This drastically simplifies sample preparation, as only pressing the sample and ID spike into pellets is required. The isotope-enriched solid can be prepared by adding isotope-enriched solution to a certified reference material containing small amounts of the analytes, shaking the resulting slurry to homogenize it, drying it, grinding it in a mortar, and finally pressing it into a 3 mm diameter pellet (without binder) (148, 149). The resulting solid, which is stable for at least 4 months (148), can be used for the analysis of a number of samples, as analyte/spike ratios within a factor of 10 of the desired 1:1 ratio still result in low uncertainty (149). Under these conditions, the resulting aerosol consists mostly of linear agglomerates of nanometer particles with only a few large spherical particles having a diameter <225 nm (149).

In fact, the particle size distribution of the aerosol produced by ablation of a 2 mm wide, 75 µm deep lane with this high repetition rate femtosecond laser, which contained 38% in mass of particles smaller than 1 µm, was similar to that produced by ablation of a 0.12 mm wide, 285 µm deep lane with a nanosecond laser (150). Reducing the ablated surface to a 0.12 mm wide lane shifted the particle size distribution such that up to 77% in mass of particles were then smaller than 1 µm (150). Furthermore, visualization of the brass aerosol particles using light scattering with a pulsed laser source revealed that particles produced by high repetition rate infrared femtosecond LA were captured in a characteristic macroscopic flow pattern consisting of well-separated filaments (151). As a result, only around 1% of particles that got in contact with the ablation cell were lost (151). A separate study indicated that 75–95% of particles was transported out of the ablation cell, whether Ar or He was used as the carrier gas (152). The ablation yield could be decreased with either extreme defocusing or tight focusing of the laser beam on the sample surface if the fluence stayed above the threshold for LA (152).

**Fractionation.** As elemental fractionation is the Achilles’s heel of LA-ICPMS, numerous studies focused on trying to get a better understanding of nonstoichiometric effects, which may arise during aerosol formation, aerosol transport to the ICP, and within the ICP. For instance, energy dispersive X-ray spectrometry and scanning electron microscopy analyses of the aerosol produced during the ablation of Co-cemented tungsten carbides revealed that large spherical particles were significantly enriched in W and their surface mostly covered with condensed Co whereas small clusters were enriched in Co (153). This is in accordance with the theory of particle formation that predicts that small particles, formed by nucleation and condensation, can be enriched in a more volatile element, whereas larger particles, which are ejected from melted liquid by the expanding vapor plume, can be richer in low-volatility elements (153).

Time-resolved studies of the LA process demonstrated that sample morphology and the type of carrier gas affected both the analyte signal and the number of spikes in it (154). For instance, many more spikes were evident in the analyte signal from pellets of dust than from a glass; although adding a binding agent reduced the number of spikes, heterogeneity of the sample pellet also introduced an additional signal variation (154). Spikes in MO⁺ signal were not only significantly less frequent than in the corresponding M⁺ signal but were also not correlated to the latter because the MO⁺ region is smaller than that of M⁺, i.e., the latter is mostly formed at the expense of the former (154). Reducing the laser pulse width from 5 ns to 370 fs significantly reduced the number and size of positive spikes in the analyte signal, as did increasing the laser rastering rate (155). Using He instead of Ar as a carrier gas reduced the number of spikes because the high thermal conductivity of He suppressed the coalescence of particles into larger ones by efficiently removing energy from the ablation site. On the other hand, because He is much lighter than Ar, it could not efficiently carry medium and large aerosol particles, which translated into a sacrifice in steady-state signal (154). Nonetheless, the detection efficiency, i.e., the ratio of ions reaching the detector over the number of atoms released by LA, is greater with He than with Ar and is essentially independent of laser wavelength and pulse duration (156).

Light scattering can be used to visualize the aerosol over a cross section of the transfer tube at the exit of a conventional ablation cell. One such study revealed that aerosol transport was dependent on the in-cell flow conditions (i.e., laminar vs turbulent) as well as the carrier gas and its flow rate (157). When a laminar flow of He is used in the cell, dispersed particles accumulated at the boundary of vortex channel flows along the tube axis with larger fragments moving inside, the latter degrading the accuracy of silicate glass analysis through significant density fluctuations in the ICP and increased elemental fractionation (157). This problem disappeared with turbulent in-cell flow, which almost completely homogenized the aerosol. It was not observed with an Ar aerosol carrier gas, which efficiently dispersed the aerosol,
irrespectively of the flow conditions that could be simulated by computational fluid dynamics (157).

A Faraday-strip array detector installed on a Mattauch—Herzog mass spectrometer with an ICP ion source is also extremely valuable for monitoring elemental fractionation when using LA. For instance, the time-integrated analyte signals following LA of brass revealed that many Zn signal spikes caused by particles were not correlated to Cu signal spikes (74). This indicates that the proportions of these elements varied between particles generated, although it does not indicate if this elemental fractionation occurred during LA, particle transport, or vaporization/ionization in the ICP (74). Monitoring element ratios during successive single femtosecond LA shots revealed that fractionation could be observed in the first laser shots, especially with a laser fluence near the ablation threshold of the sample, before stoichiometric sampling was achieved (158). Because elemental ablation probability was correlated to an element’s FIP, negligible fractionation was observed between elements with similar FIP (158). Stoichiometric sampling could also be achieved in fewer shots with higher laser fluences (158). Hence, using the highest possible laser energy was recommended to minimize volatility effects, at least when using transparent glasses to calibrate for nontransparent ones and vice versa (87). Furthermore, in addition to matching the internal standard to the analyte in terms of mass and FIP, matching in terms of temperature of condensation was also reported to be important in the case of refractory elements (87).

Another study focused on the fractionation of alkalis in synthetic anesite glasses and revealed that a significant part of the fractionation occurs on the ablation site, according to the composition of the ejecta blanket and depth profiling data below the laser crater (159). The extent of fractionation was dependent on analyte concentration and sample matrix and may depend on sample orientation in the case of crystalline matrixes because of thermal effects in different crystallographic orientations (159). As the spatial distributions of Si and Ca were differently affected by thermal effects near the ablation crater, selecting one of them as an internal standard should be done carefully, as it can affect the precision and accuracy of quantitative analysis by LA-ICPMS (159). On the other hand, no temporal elemental fractionation was observed during the ablation of carbonates, where particles are formed by photomechanical fracturing, in contrast to the ablation of silicates, where particles are formed by hydrodynamic sputtering, which suggests that fractionation arises from this latter ablation process (160).

The effect of the repetition rate of an infrared femtosecond laser on fractionation effects was investigated (147). Comparison of the Zn/Cu ratio measured with a dry and a wet ICP indicated that Zn was better ionized in the wet plasma. Enhanced sensitivity was also observed for all elements, albeit with higher background signals at m/z 29, 42, 55, and 58, which indicates the greater robustness of the wet ICP (147). Hence, the robustness of a dry ICP is too poor to even handle the improved particle size distribution obtained with femtosecond LA (147). With a robust wet ICP, particle-size-related fractionation could be reduced by using a high repetition rate along with a high scanner speed, which effectively diluted large particles from the surface with fine particles ablated from deeper levels (147).

Ablation Cells. To get around the sample size limitation of conventional LA cells, an open cell was designed, which does not contact the sample surface, fully excludes atmospheric gases, can accept samples of any size or number, has a low gas consumption with a washout <3.6 s, and provides good reproducibility and sensitivity (161). It relies on two concentric annular gas flows that are separated by a 100 µm thick annular flow restrictor and sit over an array of 18 µm holes through which microjets of gas provide a quasi-laminar flow. An outer N2 flow acts as a curtain to exclude atmospheric gases from the cell, while an inner He flow provides an inert atmosphere and acts as carrier gas through a 0.63 cm² inner ablation cell that is located 200 µm from the sample surface (161).

Modifications that were made to an ablation cell to enable a study of the composition of the aerosol generated by LA would be very useful for high spatially resolved analysis. Indeed, positioning the outlet nozzle 1 mm above the sample surface and directing the inlet nozzle tip perpendicular to the bottom of the cell reduced the signal peak width from a single laser shot by a factor of 12 and increased its peak height by a factor of 13.5 (162). Furthermore, sample washout was reduced to about 2 s, irrespective of the size of the ablation cell (162). Another group also reported the benefits of sampling the aerosol just above the sample surface. They described simple modifications that can be made to a conventional circular cell to transform it into a high-efficiency cyclonic one: extend the 2 mm outlet nozzle so that it is positioned some millimeters above the sample surface and move the inlet on the side (163). The He carrier gas is thus introduced tangentially to the radius and perpendicularly to the axis of the cell, which effectively prevents particles from touching the walls, as they are quickly carried in a laminar spiral flow toward the outlet (163). For a brass sample, 100% sample transport efficiency was achieved with 30 ms peak width at 10% peak height for Cu, which translated into enhanced sensitivity and a lower detection limit (163). The approach was also successfully applied to the measurement of seasonal variation in wood composition across a tree core (163).

A homemade 3 mL ablation cell in the form of a teardrop, which results in a high-density particle stream from a single pulse of a 193 nm laser, with only about 0.5 s washout, was used for Pb/U geochronology by LA-MC-ICPMS (164). By integration of the baseline-subtracted transient signal, the effect of differing detector response times was completely eliminated. This allowed the measurement of 206Pb/238U with 2% external reproducibility (based on 2 standard deviations) if a similar amount of material was ablated as in the standard ablation mode, which increased up to about 5% if only about 14 ng of zircon was consumed (164). Furthermore, monitoring consecutive laser shots on the same ablation spot allowed depth profiling with a resolution of around 0.1 µm/shot, which was heretofore beyond the spatial capability of laser-based methods (164).

Aerosol Transport and Processing. The common practice of daily replacement of the transfer tube between the LA cell and ICPMS to minimize memory effects may be revisited, especially if a polyvinylchloride or nylon tube is used in combination with a dry plasma. Indeed, the release of hydrogen- and oxygen-containing compounds from new tubes can cause signal enhancement and significant drift in elemental ratios over as long as 1.5–2

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h, effects that are not observed if a wet plasma is used \((165)\). These effects were also not observed with a dry plasma when using Teflon and copper tubes, although only the latter provided length independent aerosol transport (at least over 1–9 m) \((165)\).

A new connector for addition of Ar makeup gas to the He effluent from the ablation cell was designed, which resembles a sheathing device, where the sample flows through a central tube and argon is introduced through a concentric frustum tube so as to preserve a laminar flow \((166)\). Indeed, a typical transport tube, where argon is added through a Y-connector, induces turbulences \((167)\), which increase washout time. With the insertion of the connector close to the exit of the ablation cell, a laminar flow is preserved, which translates in a 140 ms washout time (i.e., for the signal to drop to 3% of the peak height) \((168)\). Such improvement should be very beneficial to high repetition rate LA applications, such as those involving imaging or depth profiling.

One way to completely eliminate the problems associated with a transport tube is to perform in-torch LA. However, a detection system with fast data acquisition capability is then required to allow multielement monitoring. One such system, involving TOFMS, was built in house, which allows the simultaneous measurements of elements across the mass range with a 30 \(\mu\)s time resolution \((168)\). When applied to the ablation of brass, a Zn/Cu ratio of only 0.08 was measured, indicating that a substantial portion of the Zn-rich aerosol fraction was lost somewhere. However, as this approach is in its infancy, further optimization is warranted, as it would be invaluable for the analysis of very small objects.

The performance of LA-ICPMS can be enhanced by adding 5 mL/min \(N_2\) to the carrier gas just before its introduction into the ICP, which is operated at increased power \((169)\). Indeed, a 2- to 3-fold improvement in sensitivity was observed for most of 65 elements (3–4-fold for S, As, and I) with a concurrent reduction in the ThO\(^{+}/\)Th\(^{+}\) ratio by 1 order of magnitude and a decrease in the ArH\(^{+}\)/Ar\(^{+}\) ratio by up to a factor of 3 \((169)\). On the other hand, doubly charged ion formation was exacerbated: the Ca\(^{2+}/\)Ca\(^{+}\) ratio increased from 0.47% to 0.63% without and with nitrogen, respectively \((169)\). These observations were ascribed to improved energy transfer between the plasma and central channel in the presence of nitrogen. However, the fact that spatial analyte ion distributions were not symmetrical in the presence of nitrogen, especially at high sampling depth, whereas those with an Ar ICP were suggested that a secondary discharge may also be involved, especially since this work was conducted on an Agilent ICPMS instrument, which requires the use of a shielded torch to decrease the potential between the plasma and the interface. It was demonstrated in the early days of ICPMS that a secondary discharge, which would be exacerbated by nitrogen, decreases oxides and increases doubly charged ions. Such uncontrollable discharge would also likely distort spatial profiles. In any case, whatever the explanation, this approach would be greatly beneficial for many applications, such as when the small ablation pit size requires enhanced elemental sensitivity for multielemental determinations \((169)\).

An alternative is to employ near-field LA, where the tip of a 100–250 nm diameter Ag needle placed about 100 nm from the sample enhances the incident light energy \((170)\). When applied to a brass sample, the Cu signal was enhanced 6-fold compared to what was observed under identical conditions without the needle \((170)\). The diameter of the resulting crater ranged between 200 nm and about 2 \(\mu\)m, depending on the needle used and the distance between the needle and the sample surface \((170)\). This nonetheless demonstrates that profiling with a resolution in the nanometer range is now possible \((170)\). It is also possible to improve the lateral resolution of any LA profile by applying deconvolution procedures to the transient data generated when neighboring ablation sites overlap so as to retrieve additional information \((171)\).

**Applications.** Despite the limitations, LA-ICPMS is increasingly used, as evidenced by Table 3, which only gives some examples of quantitative applications. When combined to MC-ICPMS, LA also enables the direct measurement of isotope ratios in solid samples, which can assist in forensic applications or in identifying the source of elements whose isotopic distribution varies in nature, to give but two examples. For instance, the history of uranium processing and emissions can be inferred from variations in measured isotope signatures in uranium oxide grains retrieved from contaminated soil and dust samples \((178)\). Imaging, i.e., mapping, of elemental distributions in thin tissue sections, plant tissues, or in the proteins that were separated orthogonally by blue native-polyacrylamide gel electrophoresis can be performed by LA-ICPMS \((179, 180)\). Although time-consuming, as it can take several hours, depending on the size of the area to be ablated, it enables new studies of transport processes and bioavailability. A complementary technique, such as MALDI-TOFMS, is also required for protein identification \((180)\).

LA-ICPMS can also be used to facilitate and enhance immunoassays. For example, proteins can be labeled with 2-(4-isothiocyanatobenzyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid sulfate polyacrylamide gel electrophoresis and electroblotted onto nitrocellulose membranes where the immuno-reaction with labeled antibody was carried out. Following drying, LA-ICPMS was used to detect the lanthanide. Monoisotopic ones, such as Eu, Tb, Tm, and Ho, were used so that the highest sensitivity could be reached, which was similar to that achieved by chemiluminescence detection \((182)\). However, the LA-ICPMS approach is less time-consuming and provides multiplexing capabilities, which was demonstrated by the simultaneous detection of three differentially labeled antibodies in a single Western blot assay \((182)\). 

**Calibration.** A common calibration strategy for the analysis of glasses is to perform an external calibration with internal standardization using an element whose concentration must be determined by an independent technique, which substantially reduces sample throughput. A simple yet effective alternative is to perform a so-called sum normalization calibration technique, which involves summing the concentrations of all matrix-containing elements as their oxides, normalizing to 100% (w/w) using...
Table 3. Selected LA Quantification Methods

<table>
<thead>
<tr>
<th>analytes</th>
<th>sample matrix</th>
<th>sample preparation</th>
<th>instrumentation</th>
<th>calibration strategy</th>
<th>feature</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>V, Cr, Cu, Fe, Ni, Zn, Cd, Sn, Pb</td>
<td>fuel oil; crude oil</td>
<td>add metallo-organic ID spike in MIBK; pipet sample onto Kleemex tissue; cover with 2.5 µm thick Mylar foil</td>
<td>SFMS (R = 4000); shielded torch; Nd:YAG 1064 nm; 25 mL/min Ar carrier to cyclonic glass chamber</td>
<td>ID</td>
<td>isotope ratio precision (1.3% RSD for Pb) degraded to 3.7% when 9 elements determined; mean isotope ratio across transient peak used for quantitation</td>
<td>172</td>
</tr>
<tr>
<td>17 elements</td>
<td>Au artifacts</td>
<td>20 laser shots used to clean sample surface</td>
<td>QMS with DRC; Nd:YAG 213 nm; LA effluent mixed with Ar in glass mixing bulb</td>
<td>EC with matrix-matched solids + 100% normalization procedure</td>
<td>similar results with nanosecond and femtosecond LA but uncertainty lower with femtosecond accurate solution calibration possible if standard solutions are matrix-matched to sample highest laser energy minimizes effects; sample transparency leads to matrix-dependent elemental fractionation for volatile elements drastically reduces sample preparation to &lt;10 min as well as total analysis time</td>
<td>173</td>
</tr>
<tr>
<td>17 elements</td>
<td>Au artifacts</td>
<td>20 laser shots used to clean sample surface</td>
<td>SFMS (R = 10 000); femtosecond-LA 263 nm; solution mixed with He effluent</td>
<td>solution EC with Cu IS; 1.5% HCl blank with LA for constant conditions</td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>many elements</td>
<td>geologic glasses, silicate glasses</td>
<td></td>
<td>SFMS (R = 400 and 4000); nanosecond-LA 213 nm; carry gas?</td>
<td>matrix-matched EC with IS having similar temperature of condensation as analyte</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu, Zn, Sn, Pb</td>
<td>soils and sediments</td>
<td>sample mixed 1:1 with isotopically enriched solid; homogenized 5 min in agate mortar; pressed into 3 mm diameter pellet</td>
<td>QMS; femtosecond-LA 1030 nm; He carrier gas; cyclic chamber to homogenize LA aerosol; 2-inlet torch used to mix LA aerosol with nebulized aerosol</td>
<td>solid-spiking ID</td>
<td>high repetition rate and fast scanning between sample and ID spike ensures their complete mixing; sample preparation &lt;5 min</td>
<td>148</td>
</tr>
<tr>
<td>Cu, Zn, Sn, Pb</td>
<td>soils and sediments</td>
<td>sample pressed into 3 mm diameter pellet (without binder)</td>
<td>QMS; femtosecond-LA 1030 nm; He carrier gas; cyclic chamber to homogenize LA aerosol; 2-inlet torch used to mix LA aerosol with nebulized aerosol</td>
<td>in-cell ID with isotopically enriched solid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54 elements</td>
<td>ancient and historic glasses</td>
<td>samples and standards mounted several mm apart on a glass slide with double-sided tape</td>
<td>QMS; nanosecond-LA 213 nm; 0.95 L/min He carrier gas; 0.75 L/min Ar makeup gas</td>
<td>sum normalization to 100% w/w (oxide concentration) with SiO2, IS</td>
<td>instrument tuned so that 219Hg/204Hg = 1 to minimize particle-induced elemental fractionation</td>
<td>174</td>
</tr>
<tr>
<td>16 elements</td>
<td>Cu, Cu powder, Mg alloy</td>
<td>powder pressed into pellet; others turned on a lathe before analysis</td>
<td>SFMS; LINA-Spark (1064 nm); Ar carrier gas; balloon for pressure compensation; spray chamber to remove large particles</td>
<td>EC</td>
<td>4 mm ablation spot; results statistically equivalent to those by GD-MS and LA-ICP-OES with the same LA system stoichiometry; measurement; better precision in raster mode (more representative sampling)</td>
<td>175</td>
</tr>
<tr>
<td>Ag, In, Sb, Te</td>
<td>Ag(In)SbTe phase change materials</td>
<td>preablation to clean the sample surface</td>
<td>QMS; nanosecond-LA 193 nm; He carrier gas; Ar makeup gas</td>
<td>EC and 100% normalization (sum of 4 concentrations used as IS)</td>
<td></td>
<td>176</td>
</tr>
<tr>
<td>multiple elements</td>
<td>biogenic carbonates</td>
<td></td>
<td>QMS; nanosecond-LA 213 nm; He carrier gas; Ar makeup gas</td>
<td>matrix-matched EC with calcite powder pellet</td>
<td>matrix-matched EC is only required for certain elements with 193 nm LA</td>
<td>160</td>
</tr>
<tr>
<td>10 elements</td>
<td>transparent glass</td>
<td></td>
<td>QMS; femtosecond-LA 266 nm; Ar carrier and makeup gas</td>
<td>EC with opaque glass standard and 48Ca IS</td>
<td>10 µm spot size at 1000 Hz repetition rate and a scan speed of 200 µm/s allow bulk analysis with good lateral resolution</td>
<td>177</td>
</tr>
</tbody>
</table>
conventional method using Si, Ca, or Fe as an internal standard (183).

As the availability of solid calibration standards limits quantitative analysis by LA-ICP-MS, an attempt was made to fabricate standards using a sol–gel process (184). Xerogels are simply prepared by mixing silica alkoxides with water, acid, and methanol, along with standard solutions of analytes to be incorporated. The mixture is poured into molds that are then covered with pierced paraffin to control evaporation. Although gelation occurs within 24 h, constant mass is reached after 14–21 days. The resulting glasslike product is colorless with no visible heterogeneity if the combined maximum concentration of S and Se does not exceed 3% and no more than 0.01% of transition metals heterogeneity if the combined maximum concentration of S and Se does not exceed 3% and no more than 0.01% of transition metals is present. With greater amounts, precipitation and hence heterogeneity result (78). These sol–gels, which are more homogeneous than NIST glass certified reference materials (CRMs), are suitable calibration standards for the analysis of glasses and silicate matrixes containing low levels of analytes but would not be suitable for the analysis of sulfides (78). They thus constitute a cheap alternative to glass CRMs.

HYPHENATION TO ELECTROTHERMAL VAPORIZATION

Coupling the capabilities of electrothermal vaporization (ETV) to deal with complex matrixes and to directly handle solids with the high sensitivity of ICPMS gives a technique that has been extensively investigated, as attested by two critical reviews (185, 186). Examples of very challenging analytical applications that it can handle are speciation analysis when different species have different volatilities, thermal resolution of spectroscopic (even isobaric!) interferences when the interfering element has or can be made to have a different volatility than the analyte, and the direct analysis of slurries and solid samples (185, 186). One of these reviews even includes a reference guide on how to do method development in ETV-ICPMS (186). With the commercial availability of an ETV unit (from Spectral Systems), there is thus no more excuse for not further exploring the multiple capabilities of this technique!

With dependence on the type of mass spectrometer (Q, with or without C/RC or DRC, TOF, SF), different advantages are obtained (186). Although optimization of the ETV temperature program with or without the addition of chemical modifier can drastically reduce the risk of spectroscopic interference, as the solvent is usually evacuated during the drying step, which substantially reduces oxide and hydroxide ions formation, and at least a portion of the matrix is eliminated during the ashing step, the formation of carbon-based polyatomic ions can complicate the determination of elements, such as Cr and Si, which require a high vaporization temperature at which covaporization of graphite is important (187). The use of ICP-SFMS in medium mass resolution is sufficient to eliminate these spectroscopic interferences on several isotopes of the analytes, in turn allowing ID, which compensates for the matrix effects observed during direct solid analysis (187).

If the matrix has a significantly lower volatility than the analytes, then direct solid analysis can be carried out with a short ETV temperature program, without the need for a pyrolysis step and vaporization simply being held at a temperature lower than the melting point of the matrix (188). As most of the matrix is then left behind, calibration with aqueous standards then becomes feasible. Although an argon dimer can be continuously monitored along with analyte ions for evidence of suppression effects, it would not indicate if other effects occur, such as thermal overstabilization of analytes in the graphite tube, which would then require IS (188). Nonetheless, even if that is the case, the possibility of using aqueous standards for the direct analysis of solid samples is a clear asset of ETV-ICPMS. An alternative to placing solid sample in a graphite cup that is then inserted in the graphite furnace is to prepare the sample as a slurry, which can then be injected just like a solution. However, a simple external calibration with aqueous solutions is not likely to be sufficient, especially with carbon-containing matrixes such as biological samples, coal, and coal fly ash, because, depending on the pyrolysis temperature, carbon particles may act as physical carriers and they may also induce enhanced analyte ionization in the plasma (189).

Because of the microsample-handling capability of ETV, it can be combined to microextraction techniques to further lower detection limits through the analyte preconcentration that is achieved along with matrix separation. For example, single-drop microextraction can be used to sample the headspace above a sample following the addition of a chemical vaporization reagent to the sample, and the drop containing the collected chemical vapor is then simply injected into the ETV unit (190). Also, analyte preconcentration and simultaneous matrix separation can be carried out with polymer monolith microextraction in a capillary, which requires only 400 µL of sample (191). This latter approach, with a bimodal porous N-(2-aminoethyl)-3-aminopropyl-trimethoxysilane-silica monolithic capillary that was prepared by sol–gel technology, can also be applied to study the fractionation of aluminum in rainwater and fruit juice, as labile monomeric Al (such as free Al$^{3+}$ and its hydroxides) is retained but nonlabile forms (such as Al complexes) (192).

Furthermore, ETV can be combined with approaches that rely on an organic solvent because the latter will be ashed in the furnace prior to analyte vaporization. For instance, the so-called “solvent bar” microextraction approach involves filling a short hollow fiber membrane with organic solvent and stirring it in the sample solution for a given length of time to allow selective extraction of analyte–reagent complexes into the solvent, which is then injected into the furnace (121). A green alternative to organic solvents involves the use of an ionic liquid as solvent, which is nonvolatile and nonflammable unlike organic solvents, for single drop microextraction (193). Table 4 summarizes some examples of quantitative applications.

HYPHENATION TO PARTICLE-SIZING TECHNIQUES

With the growing awareness of the impact of colloids and nanoparticles in the environment, techniques are being developed for the quantitative characterization of metal-containing natural colloids and synthetic nanoparticles. One such approach is asymmetric flow field-flow fractionation coupled to ICPMS, where separation takes place in a thin ribbonlike flow channel under a perpendicular crossflow of carrier fluid, which slows down large particles more than small ones (194). However, to get reproducible hydrodynamic size calibration, channel flow fluctuations must be compensated, which can be achieved by merging the effluent
with an internal standard (Rh) solution. With the use of this approach, the interaction of Eu, U(VI), and Th with a mixture of humic acid and clay colloids could be studied, and synthetic CdSe/ZnS-mercaptopropanoic acid core/shell-coated quantum dots were characterized (194).

An alternative approach is hydrodynamic chromatography (HDC), which solely separates 5–300 nm nanoparticles according to their size and requires no aqueous sample pretreatment (195). Separation occurs through a column packed with nonporous particles, which cannot be carried out with ionic standards and would likely require standards of different sizes and concentrations of analyte nanoparticle, which are not currently available (195).

A completely different approach involved coupling air-based nanoelectrospray, macroion mobility spectrometry (with an Ar sheath gas), and condensed particle counting (CPC) and ICPMS. The aerosol droplets produced by nanoelectrospray are converted into neutral and singly charged solvent-free nanoparticles in a neutralization/charge reduction chamber, which are then separated according to their gas-phase electrophoretic mobility diameters in a differential ion mobility spectrometer (IMS). The nanoparticles of increasing size that sequentially exit the latter are then counted in the CPC and simultaneously analyzed by ICPMS by splitting the IMS effluent with a tee (196). This approach allows sizing nanoparticles with a 3–100 nm electrophoretic mobility diameter (and even larger) or biomolecules with 8–80 MDa relative molecular mass (196). It was used for the simultaneous sizing of CsI and dimethylarsinic acid in solution and determination of Cs, I, and As (196). On the other hand, the ICPMS detection limit was not sufficient for the determination of the metal, metalloid, or halogen content of protein. However, the detection and accurate sizing of femt mole levels of proteins was possible through the detection of their CsI adducts (following addition of CsI), whose signal increased linearly with the amount of protein (196).

Diane Beauchemin received a B.Sc. in Chemistry from Université de Montréal and then a Ph.D. in Analytical Chemistry from the same institution at the end of 1984 (under the supervision of Joseph Hubert). After working as a Research Associate in the Institute for National Measurement Standards of the National Research Council of Canada, she moved to Queen’s University in 1988 and was eventually promoted to Full Professor (in 2001). She is interested in all aspects of ICPMS, from fundamental studies on matrix effects and mixed-gas plasmas, to environmental and biomedical applications (including chemical speciation analysis and the determination of bioaccessibility).

LITERATURE CITED
