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TIMS versus multicollector-ICP-MS: coexistence or struggle for survival?

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When J.J. Thomson discovered the isotopic nature of neon in 1912 using a self-constructed mass spectrograph [1] it was difficult to foresee what impact stable isotope analysis would have in the natural sciences over the following decades. By using isotopically enriched compounds, quantitative analysis can be performed at the highest accuracy by following isotope dilution principles. The same principles can be employed to make use of stable isotopes as tracers in complex systems including the human body. Information on the origin and history of a sample can be obtained by studying natural changes in the isotopic composition of an element induced either by radionuclide decay or by isotope-selective transport processes between physical or chemical compartments. In either case, improvements in precision, sensitivity and accuracy in isotopic analysis have in the past opened new doors in basic and applied research.

Among the plethora of mass spectrometric techniques developed in the 20th century, thermal ionization mass spectrometry (TIMS) has established itself as the reference technique for high-precision isotope ratio measurements of the heavier elements. As an example, most IUPAC recommendations for the standard atomic weights are based on isotope abundance measurements by TIMS [2]. The potential of inductively coupled plasma mass spectrometry (ICP-MS) for isotopic analysis was recognized soon after it was launched as a new tool for elemental analysis in the 1980s [3]. However, it took years to make use of this potential by overcoming major technical limitations immanent to the plasma ion source. Besides the ion species of interest, other atomic and molecular ions are formed in the plasma which can potentially interfere with the ion signals of interest. By using a double-

cussing magnetic sector field, mass spectrometric resolution can be increased to resolve molecular isobaric interferences in the mass spectrum [4]. Other approaches developed so far involve the suppression of interfering molecular ions either by collision with a residual gas in a collision cell [5], gas-phase reactions in a dynamic reaction cell [6] or a careful control of plasma conditions. By using, in addition, a multicollector device (MC-ICP-MS) for ion detection, another limitation of the plasma source for isotopic analysis could be overcome [7]. Flickers in signal intensity are significant in ICP-MS and limit the precision in the isotope ratio measurement when jumping between peaks. In MC-ICP-MS, these flickers simply cancel out as ions are detected simultaneously.

Recent instrumental developments made MC-ICP-MS competitive to TIMS as the reference technique in the field. MC-ICP-MS allows isotope ratio measurements for various elements at precisions below 50 ppm, which was previously only possible by using TIMS. At the same time, isotopic analysis is less time consuming. For TIMS analysis, the sample has to be separated from the matrix, presented in a solid state to the mass spectrometer and heated carefully to obtain a stable ion beam. On the other hand, by using a plasma ion source, the sample can be presented directly in solution or as an aerosol to the instrument, which can make sample digestion superfluous (e.g. when using a laser beam for direct sampling). In addition, ionization efficiencies are usually higher when using ICP-MS which makes it even more sensitive. Considering the obvious advantages of MC-ICP-MS over TIMS it seems as if TIMS has become superfluous. In recent years more than 80 MC-ICP-MS systems have been sold worldwide. Surprisingly, about 60 MC-TIMS instruments have also been sold in the same period and at a similar price. Is this just a belief in traditions or is scepticism growing as to whether MC-ICP-MS can keep its promises?

The precision and accuracy of an isotope ratio measurement by any mass spectrometric technique is limited by mass-dependent isotopic fractionation of the sample during analysis. Isotope fractionation effects can be introduced during ion generation, mass separation or ion de-

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tection and often show a drift with time over the course of the measurement. In fact, not a single mass spectrometric technique exists which is free of isotope fractionation effects and, therefore, delivers the true isotope ratio of the sample. Generated data can be corrected by determining the instrumental bias using gravimetrically prepared mixtures of highly enriched isotopes (calibrated measurements). For elements having three or more stable isotopes, such a mixture of known isotopic composition can be added to the sample to correct for isotopic fractionation effects (double spike technique) or measured data can be normalized to a known isotope ratio in the sample by applying theoretically or empirically derived correction laws. In general, TIMS is less susceptible to isotopic fractionation than ICP-MS. Fractionation effects in TIMS are usually in the order of parts per thousands, relatively stable and systematic, while isotopic fractionation in ICP-MS, commonly referred to as mass bias, can be easily in the percent range and depend on instrument settings and time [8].

But how can isotope ratios be measured by MC-ICP-MS at a precision and, ideally, accuracy of 50 ppm or better if the mass bias is higher by 4 orders of magnitude and even fluctuating? Different techniques are in use including a) internal normalization of measured isotope ratios [9] and double-spiking [10] as employed in TIMS, b) standard sample bracketing techniques using an isotope reference material [11] and c) external normalization to a known isotope ratio of an element standard that has been added to the sample before analysis [12]. Although in principle all of these techniques are suitable for fractionation correction, they have their limitations. For accurate data correction, isotopic fractionation processes and fractionation laws have to be understood, at least empirically, and have to be independent from the sample matrix, analyte concentration and instrument settings. This is not the case in most situations. To perform isotope ratio measurements by MC-ICP-MS which are not only tremendously precise but also accurate, the element has to be separated as tediously from the sample matrix as in TIMS. This is necessary not only for a better control of isotopic fractionation during the measurement but also to avoid artefacts due to isobaric interferences which cannot be resolved instrumentally. It has to be noted that instrumental approaches in ICP-MS made so far reduce the risk of bias due to isobaric interferences but they still remain a major obstacle in generating meaningful isotopic data.

Even if all efforts have been made to minimize bias, use of isotopic reference materials is mandatory. However, it is a severe misconception to assume that a MC-ICP-MS technique is validated only by showing that generated data agree well with certified or commonly agreed reference values and that referring to a published validation study is sufficient for claiming data accuracy. What was found to work for one application/instrument/sample might not be given in another situation, with external mass bias correction being a good example. Furthermore, sources of systematic bias in ICP-MS are multiple and bias effects can cancel out when analysing a reference material. At least two reference materials of different iso-

topic composition are needed to minimize the risk of an artefact. To date, no sets of isotopic reference materials for the ICP-MS community exist, with the exception of uranium (IRM-072, IRM-073) [13]. If a certified isotopic reference material is available, which is not given for a number of elements, this material commonly does not match the matrix of the samples to be analysed. This points again to the need of matrix separation to perform accurate isotope ratio measurements by MC-ICP-MS.

Quality control appears to become a major issue when looking at the potential risks of generating artefacts when using ICP-MS for isotopic analysis and the steadily growing number of scientific conclusions that are drawn from generated data. This refers in particular to applications where findings may affect legal or political decisions, for example when isotope ratio measurements are performed in food authentication, forensic analyses or nuclear safeguarding. In biomedical research, wrong conclusions may affect the individual when findings are translated into public health programs, for example when stable isotope techniques are employed for the design and/or evaluation of a government-led food fortification program. For any of these applications, it is not the value of an isotope ratio itself but the uncertainty of the measurement that decides what action should be taken. This requires more than a simple statement regarding the precision of the measurement. Possible sources of systematic bias have to be evaluated carefully and considered by expanding the uncertainty interval of the measurement.

To date, no commonly agreed guidelines exist on how to validate an ICP-MS technique for isotopic analysis and what measures of quality control should be taken when the technique is used routinely for sample analysis. As an example, three isotope plots are a useful tool to check for the absence of isobaric interferences but their use is not obligatory to prove data accuracy. For elements having at least three stable isotopes, two isotope ratios can be measured with a common reference isotope. When analysing an isotopic reference material of known isotopic composition, measured isotope ratios can be expressed on a δ -scale (i.e. as their relative deviation from the reference value in parts per thousand). When isotope ratios are plotted for the reference material against each other, as illustrated in Fig. 1 for iron, they should lie on a curve that is defined by the underlying isotope fractionation law which should depend on the isotope masses. Offsets from the curve indicate the presence of isobaric interferences. The same holds for the sample provided that the isotopic abundances are not affected by radioactive decay. Even if the element in the sample shows an altered isotopic composition due to natural fractionation processes, measured data have to lie on the fractionation curve. There is some debate as to which of the proposed laws describe fractionation processes the best [14]. However, differences between the fractionation laws are usually too small in practice to be resolved within the achievable precision of the isotope ratio measurement.

Three isotope plots are just one example of the possible approaches to confirm the accuracy of measured data. For independent evaluation of published data by the sci-

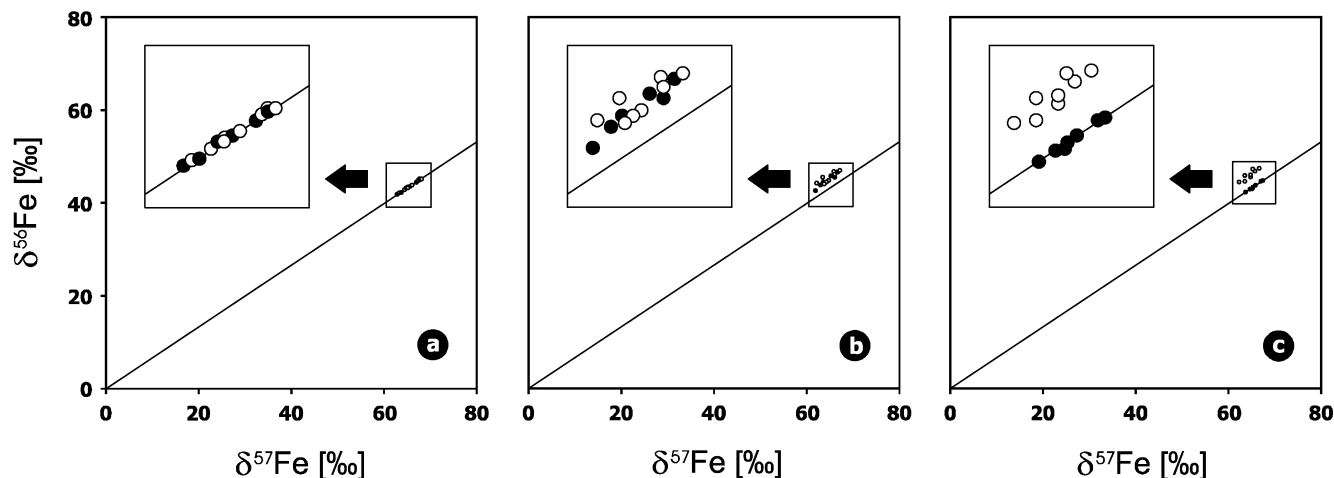


Fig. 1a–c Use of three isotope plots to check for isobaric interferences in MC-ICP-MS. Each *point* represents the mean of an iron isotope ratio measurement of a standard (●) or a sample (○) of natural isotopic composition. Isotope ratios ($^{56}\text{Fe}/^{54}\text{Fe}$ and $^{57}\text{Fe}/^{54}\text{Fe}$, respectively) are plotted on a δ -scale ($\delta^{56}\text{Fe}$ and $\delta^{57}\text{Fe}$, respectively), i.e. as relative deviations in parts per thousand from the known isotope ratio of an isotope reference material of natural isotopic composition (IRM-014). The diagonal line represents the theoretical fractionation curve as defined by the isotope masses and an exponential fractionation law. **a** Absence of isobaric interferences. Data points from standard and sample plot on the theoretical curve. **b** At least one isotopic signal in the mass spectrum of the standard and the sample is interfered. **c** Matrix differences between standard and sample result in an offset of the sample data points from the theoretical fractionation curve due to isobaric interferences

entific community, data sets from quality control measurements and experiments have to be accessible to the reader. This is usually not the case. A lack of consent within the community, limited publication space in scientific journals and a lack of stringent guidelines for data publication by journal editors often leave the reader with due scepticism if data are trustworthy and scientific conclusions can be justified. Unless firm quality control protocols are established for MC-ICP-MS measurements, TIMS will, therefore, remain as the reference technique for isotope ratio measurements of the heavier elements. However, even if these standards are hopefully established in the coming years, TIMS will still have its place in inorganic mass spectrometry. The gap between TIMS and MC-ICP-MS narrows in practical terms when taking into account the different precautions necessary to minimize the risk of generating artefacts using MC-ICP-MS. Chemical separation of the element from the matrix and the need for various quality control tests make measurements by MC-ICP-MS nearly as time consuming as by TIMS. Thus, other factors become decisive such as robustness, running costs and element-specific advantages. As an example, the high ionization potential of hafnium makes MC-ICP-MS more

suitable for this element [12]. In contrast, osmium isotope ratio measurements are technically less demanding to perform by TIMS at higher sensitivity and precision by bleeding oxygen into the ion source [15, 16]. Without question, MC-ICP-MS has opened new doors in science, in particular for studying small natural isotope fractionation effects for the heavier elements such as iron, which are difficult to measure using TIMS [17]. However, it is in the hands of the MC-ICP-MS community to make sure that it is used in the future as a key to a palace rather than a maze.

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