(i) Can and should we construct functions linking the individual isotope concentration to the instrumental parameters and propagate the uncertainties according to these functions?

ICPMS and its important branch, LA-ICPMS, use the principle of internal standardisation for data quantification[1-3]. Let us discuss a pair of two isotopes, *X* and *Y*. We perform an analysis of a standard material, of which the concentration [= mass content] ratio $\frac{c^X_{std}}{c^Y_{std}}$ is known from the standard description. As an output of this analysis, we get a mean intensity ratio $\left(\frac{I^X_{std}}{I^Y_{std}}\right)_{mean}$.

Let us now consider the equation:

$$\left(\frac{I^X_{std}}{I^Y_{std}}\right)_{mean} = \beta \frac{c^X_{std}}{c^Y_{std}} \quad \text{(i)}$$

Coefficient β, equalling the concentration ratio and the intensity ratio, is the only unknown in this equation and can be calculated. Coefficient β can be called *sensitivity ratio*. Its determination represents the main reason to apply an external standardisation in the isotope ratio and in the trace element ICPMS analysis, and is the backbone of any quantitative or semi-quantitative ICPMS technique.

Usually, we also have a sample where the concentration ratio $\frac{c^X_{sample}}{c^Y_{sample}}$ must be determined. We analyse the sample by LA-ICPMS and obtain a mean intensity ratio $\left(\frac{I^X_{sample}}{I^Y_{sample}}\right)_{mean}$. Let us consider the equation:

$$\left(\frac{I^X_{sample}}{I^Y_{sample}}\right)_{mean} = \beta \frac{c^X_{sample}}{c^Y_{sample}} \quad \text{(ii)}$$

The intensity ratio in this equation is known from our LA-ICPMS analysis of the sample. The β coefficient is not known, but we assume that it is the same as the β coefficient determined on the external standard. The only unknown is the concentration ratio, which we look for.

Combining equations (i) and (ii) leads to the well-known equation for the sample concentration ratio:

$$\frac{c^X_{sample}}{c^Y_{sample}} = \frac{\frac{c^X_{std}}{c^Y_{std}}}{\left(\frac{I^X_{std}}{I^Y_{std}}\right)_{mean}} \left(\frac{I^X_{sample}}{I^Y_{sample}}\right)_{mean} \quad \text{(iii)}$$

This equation is of general significance in the ICP mass spectrometry and remains the same for the isotope ratio and for the trace element techniques. In the latter case, *Y* can be considered as an internal standard for *X*, and its concentration in the sample must be estimated *a priori*.

It is important to note that LA-ICPMS does not attempt to construct functions as follows:

$$c^X_{sample} = I^X_{sample} \times \alpha_1 \times \alpha_2 \times \alpha_3 \times \ldots \times \alpha_k \quad \text{(iv)}$$

where factor α_1 describes a correction for the ablation yield for isotope *X*, α_2 – correction for its ionisation efficiency, α_3 - correction for ion transmission in the ion channel, etc.

The currently used LA-ICPMS quantification approach described above instead assumes that these factors are either equal for isotopes *X* and *Y*, or their ratio for isotopes *X* and *Y* remains the same for any material analysed (enabling the sensitivity ratio transfer from the standard to the sample):

$$\beta = \frac{(\alpha_1 \times \alpha_2 \ldots \times \alpha_k)^Y}{(\alpha_1 \times \alpha_2 \ldots \times \alpha_k)^X} = Const$$

Transferring the sensitivity ratio from the standard to the sample allows deriving equation (iii) for the sample concentration ratio that includes only individual intensities and their ratios; factors α are removed. In troublesome cases, a matrix matching between the sample and the matrix is used to further decrease the role of instrumental parameters hidden in these factors (i.e., in the sensitivity ratio value).

One can argue that this approach is incomplete, because it does not teach us about the interplay between instrumental parameters such as laser system parameters, detector system parameters, atomic parameters, sample parameters, environmental parameters, acquisition parameters, plasma chemistry in the laser spot, etc., and concentration (concentration ratio) we look for, and thus prevents us from progressing in the field of ICPMS.

But this argument contrasts the practice of thirty years of development in ICPMS and of twenty years of LA-ICPMS, where all quantitative data have been and still are obtained based on the internal standardisation approach, without using poorly known now and material-specific empirical or theoretical functions connecting, for example the ablation yield with the parameters of the laser beam and properties of the ablated material. It is also to neglect the practice of many decades in the field of secondary ion mass spectrometry (SIMS), where the complexity of secondary ion sputtering from crystalline solids of complex chemical composition is also approached based on the principle of internal standardisation as explained above, using a matrix matching between the standard and sample when necessary and possible[4-6], without building a quantitative model of sputtering as a function of the primary beam parameters and sample composition, structure and orientation.

This said, we are not against studies linking concentrations with instrumental parameters. But we emphasize that the current approach of quantitative LA-ICPMS and SIMS is to replace using these links, poorly known as far as the ablation yield and processes in the ICP are concerned, by the principle of internal standardisation. This is in accord with the ISO-GUM guided metrological studies available in the field of ICPMS[2].

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(ii) Can we construct functions linking the individual isotope intensity to the instrumental parameters (modelling ICPMS intensities)?

The fundamentals of ICPMS signal fluctuations are rooted in the theory of Poisson processes. To explain the role of the Poisson process in the distribution of ICPMS count numbers, we consider the Poisson distribution as a limiting case of the binomial distribution constrained by inefficient ion transmission from the ICP to the detector. The ICP is an atmospheric pressure ion source. Extracting ions from the ICP into the ion channel of the spectrometer, kept under vacuum, is a technical challenge: most ions generated in the ICP are lost during the extraction. In addition, losses due to incomplete ion transmission in the ion channel, especially at higher resolutions, should be taken into account. Thus, if a large number (M) of ions face the sampler cone per time interval, but the probability (p) for each individual ion to reach the detector and be registered is low, the numbers (N) of actually registered ions per time interval (per analysis) are Poisson distributed with a mean and variance equal to pM. This formalism is valid if the number M of ions subject to extraction per time interval is constant. However, due to turbulences in the torch and instabilities of the sample introduction system, M fluctuates with time. This is the case of the so-called doubly stochastic, or mixed, Poisson process[1]. It could be imagined that a subset of N values is acquired at one M, an other subset – at an other M, etc., after which all subsets are mixed in proportions corresponding to the probability of occurrence of a given M value[1,2]. The mixing results in the appearance of an excess variance in the distribution of

count numbers compared to the variance of an ordinary Poisson process (constant M)[1,2]. The excess variance shows a quadratic dependence on the signal intensity. In weak signals, it is insignificant. Such signals can often be adequately approximated by an ordinary Poisson process with a variance equal to the mean count number. In strong signals, it increases. The excess variance in the uncertainty of ICPMS signals is otherwise known as flicker noise, although it is an integral part of the doubly stochastic Poisson process, not an individual noise component. Describing a doubly stochastic Poisson process brings us to a mathematical formalism as follows[1]:

$$Var\{N(0,T)\} = N_{mean} + \underbrace{2\int_0^T (T-u)\gamma(u)\,du}_{excess\ variance} \qquad \text{(v)}$$

where $N(0,T)$ is the total number of counts acquired in an analysis of duration T, N_{mean} is the mean number of counts over a series of replicate analyses, and $\gamma(u)$ is the intensity autocovariance function, which indeed reflects the role of instrumental parameters, such as processes in the ICP and during the ablation. The dead time correction to the variance in this formula is omitted for simplicity, and the formula (v) is valid for non-transient signals only.

The Poisson description of uncertainty in ICPMS is a causal model describing the source of fluctuations, not only their extent. At the same time, it requires estimating the autocovariance function $\gamma(u)$, which is mathematically complex and poorly developed for *transient* signals. Given the mathematical complexity of the double stochasticity, descriptive methods based on the individual sweep intensities or their ratios are widely used and still remain the only practical solution for the uncertainty estimation of strong ICPMS signals with a non-negligible excess variance. The differencing method belongs to the family of these methods, namely it provides a practical solution for transient signals.

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(iii) If we do not have functions linking an isotope concentration or intensity to the instrumental parameters, is the combined uncertainty of the sample concentration (ratio) underestimated?

The combined uncertainty above is calculated according to equation (ii), propagating the intensity ratio and the sensitivity ratio uncertainties as explained in section 'Introduction to the methodology of the LA-ICPMS signal treatment', using equation (2) from this section:

$$Var\left(\frac{c^X}{c^Y}\right) = \beta^{-2} Var\left(\frac{I^X}{I^Y}\right)_{mean} + \beta^{-4}\left(\frac{I^X}{I^Y}\right)^2_{mean} Var(\beta)$$

This equation gives the variance of the concentration ratio c^X/c^Y of isotopes X and Y depending on the absolute values and variances of their intensity ratio I^X/I^Y and sensitivity ratio β (under the assumption of no covariance between them).

If all components in this equation have correctly estimated uncertainties, the combined uncertainty will not be underestimated. Calculating the sensitivity ratio uncertainty is beyond the scope of this paper; it invokes the certification of standard(s) and, in the current LA-ICPMS practice of isotope ratio measurements, a replicate analysis of one single standard. We assume that the sensitivity ratio uncertainty is accurately estimated, and refrain here from further discussions on this subject.

Calculating the intensity ratio uncertainty based on the ratio of means definition and using the differencing method is the subject of this paper. This is done based on the mean intensity uncertainties of the individual isotopes forming the ratio [see f-la (7) in the main text]. Is the mean intensity uncertainty underestimated if we do not consider functions linking an isotope intensity to the instrumental parameters?

The intensity of an isotope is a ratio of the number of counts to time during which those counts were collected:

$$I_{mean} = \frac{N}{t} \qquad \text{(vi)}$$

In the counting mode, this intensity is dead time corrected:

$$I_{mean\ corrected} = \frac{N_{collected}}{t - N_{collected}\tau} \qquad \text{(vii)}$$

where τ is the detection system dead time. In the current ICPMS practice, τ, if determined by the ratio method, is considered precisely known, and its uncertainty is not propagated[1-3]. Our replicate dead time measurements on the sector field ICPMS Element XR, based on the ratio method, give a scatter of no more than 1 ns, and we support the general opinion that the dead time can be considered as precisely known. Measurement time *T* is always considered to be precisely known.

The same applies to the counting-analog calibration. Intensity collected in the analog mode is recalculated as a count per second value using a calibration coefficient. Methods to calibrate such coefficients are instrument dependent; basically, they require collecting the same signal by a large number of replicate paired measurements, when the signal is first acquired in the counting mode, then in the analog mode, etc. This calibration is considered precise in the current ICPMS practice.

Thus, in ICPMS, we consider intensities as a function of the count numbers and constant values that have no uncertainties. Consequently, estimating the mean intensity uncertainty as a standard deviation of the mean for a number of dead time corrected sweep intensities does not involve parameters, which are included in the mathematical expression for the sweep intensities, but of which the uncertainties are unjustly neglected. No intensity uncertainty underestimation occurs.

For an interested reader, we could make a theoretical remark regarding the accuracy, not precision, of the dead time correction as it is commonly done in the ICPMS (f-la vii). This formula is strictly valid only for Poisson distributed signals with a constant rate (variance=mean count number). For signals, of which the rate randomly varies, such as doubly stochastic Poisson distributed signals, more complex models are invoked[4,5]. This question is beyond the current ICPMS knowledge.

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