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# Reducing the matrix effects in chemical analysis: fusion of isotope dilution and standard addition methods

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**Abstract.** The combination of isotope dilution and mass spectrometry has become an ubiquitous tool of chemical analysis. Often perceived as one of the most accurate methods of chemical analysis, it is not without shortcomings. Current isotope dilution equations are not capable of fully addressing one of the key problems encountered in chemical analysis: the possible effect of sample matrix on measured isotope ratios. The method of standard addition does compensate for the effect of sample matrix by making sure that all measured solutions have identical composition. While it is impossible to attain such condition in traditional isotope dilution, we present equations which allow for matrix-matching between all measured solutions by fusion of isotope dilution and standard addition methods.

*Keywords*: isotope dilution, standard addition, matrix effects

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## 1. Introduction

Isotope dilution is a popular method of calibration in chemical analysis when using mass spectrometry [1]. In the simplest form of all isotope dilution mass spectrometry methods, an aliquot of the sample (A) is mixed with a known amount of enriched isotopic standard (B) and the isotopic composition (isotope ratio, $R_1$) of the resulting blend is measured. From here, the mass fraction of the analyte can be obtained if the isotopic compositions of A and B are known:

$$w_{\mathrm{A}} = w_{\mathrm{B}} \frac{m_{\mathrm{B}}}{m_{\mathrm{A}}} \frac{(R_{\mathrm{B}} - R_1)}{(R_1 - R_{\mathrm{A}})} \frac{M_{\mathrm{A}} x_{k,\mathrm{B}}}{M_{\mathrm{B}} x_{k,\mathrm{A}}} \tag{1}$$

In order to obtain accurate estimate of the mass fraction of A, $w_{\mathrm{A}}$, the measured isotope ratio, $r_1$, must be corrected for systematic measurement errors known as instrumental mass discrimination. Commonly, the mass discrimination is corrected by analysing a standard solution of pure analyte, preferably one with known isotopic composition (isotopic reference materials). The measured isotope ratio of the standard, $r_{\mathrm{std}}$, is then directly compared against the tabulated values from IUPAC, $R_{\mathrm{std}}$:

$$R_1 = r_1 \frac{R_{\mathrm{std}}}{r_{\mathrm{std}}} \tag{2}$$

This approach tacitly assumes that the sample matrix has no influence on the measured isotope ratio. In other words, it assumes that isotope ratios measured from a standard solution will be biased the same way as those measured from the solutions containing the sample. However, the "standard"can be viewed as a pure single-element solution whereas "sample"- a multi-element mixture. It is a common knowledge in mass spectrometry, that the composition of the analysed sample solutions can affect the observed isotope ratios.

Similar to the above approach, some analysts measure all three isotope ratios $R_{\mathrm{B}}$, $R_{\mathrm{A}}$, and $R_1$ in order not to perform the correction for the instrumental mass discrimination at all. This strategy assumes, again, that all three measured isotope ratios will be biased the same way in order for the mass discrimination factor to cancel-out from Eq. 1. Last, instead of finding a solution to this problem through experimental design, some analysts prefer to perform analyte-matrix separation by the means of chromatography in order to eliminate the effect of the sample matrix.

The observation that isotope ratios, as measured by mass spectrometry, are affected by the sample composition has led to the development of one the most recognized calibration methods in geosciences: the double spike calibration [2]. In addition, the effect of matrix on isotope ratio measurements is well documented in inductively coupled plasma mass spectrometry [3] and electrospray ionization mass spectrometry [4]. While it is recognized that the sample matrix can have a considerable effect on the intensity of the measured signals in chemical analysis [5, 6], some even describing it as the "Achilles heel"of quantitative analysis [4], the effect of sample matrix on the *ratio* of two measured signals is considered less frequently.

This work explores the limitation of current isotope dilution equations in regards to the correction of the instrumental mass discrimination in mass spectrometry. This manuscript proposes a new class of isotope dilution strategy that is explicitly designed to withstand the adverse effects of the sample matrix when performing isotope ratio measurements. In particular, it borrows from the method of standard addition where all measurements are performed with solutions that contain nearly identical amount of the sample. Consequently, the effect of the sample matrix can be assumed constant with little to no effect on the obtained isotope ratios. The purpose of this manuscript is to put forward mathematical framework for the hybrid SA-IDMS methods applicable to both elemental and molecular mass spectrometry. We also offer brief comments on the performance of these equations recognizing that detailed study of the optimum conditions is a matter of separate study.

## 2. Theory

Consider the analyte (A), primary standard (A$*$), and the isotopically-enriched form of analyte (B). Analysing the isotopic composition of the various mixtures of these three materials forms the conceptual landscape for the proposed method. In general, we have the following amount-balance equation:

$$n_{i,\mathrm{AA}*\mathrm{B}} = \sum_{\mathrm{E}=\mathrm{A},\mathrm{A}*,\mathrm{B}} x_{i,\mathrm{E}} w_{\mathrm{E}} m_{\mathrm{E}} M_{\mathrm{E}}^{-1} \tag{3}$$

Throughout this manuscript we employ conventional

**Table 1.** Notation of symbols and quantities.

| Symbol | Description |
|---|---|
| *Materials* | |
| A | Analyte |
| A∗ | Natural standard |
| B | Enriched isotopic standard (spike) |
| E | A, A∗, or B |
| AB | Mixture of materials A and B |
| *Quantities* | |
| $w_{\mathrm{E}}$ | Mass fraction of material E in the solution |
| $m_{\mathrm{E}}$ | Mass of solution of E with mass fraction $w_{\mathrm{E}}$ |
| $M_{\mathrm{E}}$ | Molar mass of E |
| $n_{i,\mathrm{E}}$ | Amount of isotope $i$ in E |
| $x_{i,\mathrm{E}}$ | Abundance of isotope $i$ in E, $x_{i,\mathrm{E}} = n_{i,\mathrm{E}}/n_{\mathrm{E}}$ |
| $R_{\mathrm{E}}$ | Isotope amount ratio in E, $R_{\mathrm{E}} = n(^i\mathrm{E})/n(^k\mathrm{E})$ |

IUPAC notation for symbols which is summarized in Table 1. We also use the notation ID$^n$MS for the various isotope dilution strategies where $n$ denotes the number of blends (of A and/or A∗ mixed with B) measured.

Given that all isotope ratios are expressed relative to the same denominator isotope $k$, isotopic abundances $x_{i,\mathrm{E}}$ and $x_{k,\mathrm{E}}$ are related: $x_{i,\mathrm{E}} = x_{k,\mathrm{E}}R_{\mathrm{E}}$ (note that $x_{i,\mathrm{E}} + x_{k,\mathrm{E}} = 1$ for systems with only two isotopes). With this in mind, Eq. 3 provides the isotope amount ratio, $R_{\mathrm{AA*B}}$, in the ternary mixture of A, A∗, and B:

$$R_{\mathrm{AA*B}} = \frac{\sum\limits_{\mathrm{E=A,A*,B}} R_{\mathrm{E}} x_{k,\mathrm{E}} w_{\mathrm{E}} m_{\mathrm{E}} M_{\mathrm{E}}^{-1}}{\sum\limits_{\mathrm{E=A,A*,B}} x_{k,\mathrm{E}} w_{\mathrm{E}} m_{\mathrm{E}} M_{\mathrm{E}}^{-1}} \qquad (4)$$

Equation 4 forms the basis for the fusion of standard addition and isotope dilution methods and this manuscript is devoted to in-depth analysis of this equation. Note that the traditional isotope dilution and standard addition methods are based on the analysis of multiple *binary* mixtures, yet the fusion of these two methods manifests itself as the analysis of multiple *ternary* mixtures, much like the method of standard addition when combined with internal standard.

Practical implementation of the method of isotope dilution takes different degrees of complexity depending on the extent of prior knowledge of variables found in Eq. 4. We will now outline various isotope dilution approaches and provide detailed mathematical expressions for the fusion of isotope dilution and standard addition methods.

### *2.1. SA-ID$^1$MS*

Consider the simplest isotope dilution experiment with ternary mixture (A, A∗, and B) whereby all three components are admixed and the isotope ratio in the resulting mixture ($R_1$) is determined. The mass fraction of the analyte, $w_{\mathrm{A}}$, can be obtained from Eq. 4 as follows:

$$w_{\mathrm{A}} = \sum_{\mathrm{D=A*,B}} w_{\mathrm{D}} \frac{m_{\mathrm{D},z}(R_{\mathrm{D}} - R_z)}{m_{\mathrm{A},z}(R_z - R_{\mathrm{A}})} g_{\mathrm{A,D}} \qquad (5)$$

where

$$g_{\mathrm{A,D}} = \frac{M_{\mathrm{A}} x_{k,\mathrm{D}}}{M_{\mathrm{D}} x_{k,\mathrm{A}}} \qquad (6)$$

Here the sole ternary mixture is identified with the index $z$ ($z = 1$). While Eq. 5 is the general form of SA-ID$^1$MS, it can be simplified for practical needs. The analyte and the natural primary standard are frequently assumed to have the same isotopic composition, which means that A = A∗, $R_{\mathrm{A}} = R_{\mathrm{A*}}$, and $M_{\mathrm{A}} = M_{\mathrm{A*}}$. Eq. 5 then simplifies to

$$w_{\mathrm{A}} = -w_{\mathrm{A*}} \frac{m_{\mathrm{A*},1}}{m_{\mathrm{A},1}} + w_{\mathrm{B}} \frac{m_{\mathrm{B},1}(R_{\mathrm{B}} - R_1)}{m_{\mathrm{A},1}(R_1 - R_{\mathrm{A}})} g_{\mathrm{A,B}} \qquad (7)$$

with $g_{\mathrm{A,B}}$ defined in Eq. 6. One can see also that Equation 7 further simplifies into ID$^1$MS equation (Eq. 1) when no natural standard (A∗) is added, i.e., when $m_{\mathrm{A*},1} = 0$.

Note that SA-ID$^1$MS is unable to compensate for the matrix effect because it is impossible to measure $R_{\mathrm{B}}$ in the presence of sample matrix. If, however, $R_{\mathrm{B}} \approx 0$, a condition which sometimes can be met in practice, the above expression can be used to obtain matrix-matched isotope dilution results because $R_1$ and $R_{\mathrm{A}}$ can both be measured under similar conditions. In practice, however, the mass fraction of the isotopic standard, $w_{\mathrm{B}}$, not known beforehand and it has to be determined with the aid of reverse isotope dilution. This prompts many to employ double isotope dilution (ID$^2$MS) instead of ID$^1$MS.

### *2.2. SA-ID$^2$MS*

Consider the analysis of two distinct samples where A, A∗ and B are admixed in different proportions. The isotope ratio in both mixtures can be described using Eq. 4. Consequently, we obtain two equations that are analogous to Eq. 5, one equation for each of the analysed mixtures. Combining these two equations allows us to obtain the mass fraction of the analyte in the sample, $w_{\mathrm{A}}$, without the recourse to $w_{\mathrm{B}}$:

$$\frac{w_{\mathrm{A}}}{w_{\mathrm{A*}}} = \frac{\begin{array}{c} -\,m_{\mathrm{A*},1} m_{\mathrm{B},2} (R_1 - R_{\mathrm{A*}})(R_{\mathrm{B}} - R_2) \\ -\,m_{\mathrm{B},1} m_{\mathrm{A*},2} (R_{\mathrm{B}} - R_1)(R_{\mathrm{A*}} - R_2) \\ +\,m_{\mathrm{A},1} m_{\mathrm{B},2} (R_1 - R_{\mathrm{A}})(R_{\mathrm{B}} - R_2) \\ +\,m_{\mathrm{B},1} m_{\mathrm{A},2} (R_{\mathrm{B}} - R_1)(R_{\mathrm{A}} - R_2) \end{array}}{} g_{\mathrm{A,A*}} \qquad (8)$$

Eq. 8 is the general form for SA-ID$^2$MS and it can be simplified for practical purposes by assuming identical

isotopic composition between the analyte and natural standard, i.e., A = A∗ and $g_{\mathrm{A,A*}} = 1$.

A problem inherent to SA-ID$^1$MS and SA-ID$^2$MS is that the isotopic composition of the enriched isotopic standard (B) cannot be measured in the presence of sample matrix. Hence, analysts have two recourses: (1) either take "literature" values for $R_{\mathrm{B}}$ and perform the correction of instrumental mass fractionation on all other isotope ratios, or (2) eliminate $R_{\mathrm{B}}$ from measurement model. The elimination of $R_{\mathrm{B}}$ can be achieved numerically by choosing a spike which has no traces of natural isotopic signature (thus rendering $R_{\mathrm{B}} \approx 0$). If the condition $R_{\mathrm{B}} \approx 0$ cannot be achieved, one can eliminate variable $R_{\mathrm{B}}$ from the measurement model which leads us to SA-ID$^3$MS. Although the condition $R_{\mathrm{B}} = 0$ is somewhat unrealistic in elemental mass spectrometry, it is quite reasonable in molecular spectrometry. For example, the analysis of cholesterol is often done using trisilyl-[$^{13}C_3$]-cholesterol for which $R_{\mathrm{B}} = R_{458/461} \approx 1 \times 10^{-6}$.

### *2.3. SA-ID$^3$MS*

Triple isotope dilution employs isotope ratio measurements of three mixtures. The model equation for $w_{\mathrm{A}}$ is obtained by solving three equations: Eq. 5 with $z$ = 1, 2, and 3. Traditionally, the variable $R_{\mathrm{B}}$ is eliminated from the model equation in ID$^3$MS although other options are possible (elimination of $R_{\mathrm{A}}$, for example). When Eq. 5 ($z$ = 1, 2, 3) is solved for $w_{\mathrm{A}}$, $w_{\mathrm{B}}$, and $R_{\mathrm{B}}$, the following master equation for SA-ID$^3$MS is obtained:

$$\frac{w_{\mathrm{A}}}{w_{\mathrm{A*}}} = \frac{\begin{array}{r} +m_{\mathrm{A*},1}m_{\mathrm{B},2}m_{\mathrm{B},3}(R_1{-}R_{\mathrm{A*}})(R_2{-}R_3) \\ -m_{\mathrm{A*},2}m_{\mathrm{B},1}m_{\mathrm{B},3}(R_2{-}R_{\mathrm{A*}})(R_1{-}R_3) \\ +m_{\mathrm{A*},3}m_{\mathrm{B},1}m_{\mathrm{B},2}(R_3{-}R_{\mathrm{A*}})(R_1{-}R_2) \end{array}}{\begin{array}{r} -m_{\mathrm{A},1}m_{\mathrm{B},2}m_{\mathrm{B},3}(R_1{-}R_{\mathrm{A}})(R_2{-}R_3) \\ +m_{\mathrm{A},2}m_{\mathrm{B},1}m_{\mathrm{B},3}(R_2{-}R_{\mathrm{A}})(R_1{-}R_3) \\ -m_{\mathrm{A},3}m_{\mathrm{B},1}m_{\mathrm{B},2}(R_3{-}R_{\mathrm{A}})(R_1{-}R_2) \end{array}} g_{\mathrm{A,A*}} \quad (9)$$

Note that this equation can be reduced to the classical ID$^3$MS, as given by Vogl [7]. This corresponds to a situation $m_{\mathrm{A*},1} = m_{\mathrm{A},2} = m_{\mathrm{A},3} = 0$ and A = A∗.

Eq. 9 can be simplified for practical purposes by assuming identical isotopic composition between the analyte and the natural standard (A = A∗). In addition, one can encounter situations in organic analysis where the analyte does not contain any appreciable levels of the enriched isotope. An example of this is the analysis of BPA (bisphenol A) using [$^{13}C_{12}$]-BPA as a spike in which case $R_{\mathrm{A}} \approx 10^{10}$. Together, assumptions A = A∗ and $R_{\mathrm{A}} \to \infty$ reduce Eq. 9 to

$$\frac{w_{\mathrm{A}}}{w_{\mathrm{A*}}} = \frac{\begin{array}{r} +m_{\mathrm{A*},1}m_{\mathrm{B},2}m_{\mathrm{B},3}(R_2 - R_3) \\ -m_{\mathrm{A*},2}m_{\mathrm{B},1}m_{\mathrm{B},3}(R_1 - R_3) \\ +m_{\mathrm{A*},3}m_{\mathrm{B},1}m_{\mathrm{B},2}(R_1 - R_2) \end{array}}{\begin{array}{r} -m_{\mathrm{A},1}m_{\mathrm{B},2}m_{\mathrm{B},3}(R_2 - R_3) \\ +m_{\mathrm{A},2}m_{\mathrm{B},1}m_{\mathrm{B},3}(R_1 - R_3) \\ -m_{\mathrm{A},3}m_{\mathrm{B},1}m_{\mathrm{B},2}(R_1 - R_2) \end{array}} \quad (10)$$

In SA-ID$^3$MS, all isotope ratios can be measured under similar conditions, i.e., in the presence of equal amounts of the sample matrix. Consequently, the effect of the sample matrix can be eliminated. The major assumption that the analyst has to make is that A = A∗. This assertion should be made with care for all those elements whose isotopic compositions are known to vary in nature. For example, isotope ratio of boron, $n(^{11}\mathrm{B})/n(^{10}\mathrm{B})$, differs approximately by five percent from seawater to commercial reagents [8]. Thus, when seawater samples are analyzed using commercial reagents (boric acid) as primary standards, errors can arise from the assumption of identical isotopic composition between samples and standards.

### *2.4. Higher order SA-IDMS methods*

We have shown before that IDMS models can be extended to higher orders, such as ID$^4$MS [9]. Similarly, it is possible to construct higher order SA-IDMS methods but the corresponding model equations become too complex. Given that the utility of SA-ID$^2$MS and SA-ID$^3$MS models has not yet been demonstrated experimentally, we refrain here from providing expressions for SA-ID$^4$MS or higher methods and reserve this for a later publication.

## 3. Discussion

The development of isotope dilution equations has been focused towards eliminating the hard-to-measure variables. For example, the isotopic composition of enriched spike, $R_{\mathrm{B}}$, is hard to measure as it is affected by the blank contamination and carry-over effects. Consequently, ID$^3$MS was developed because it eliminates the need to know or measure this variable [7]. Building from this tradition, as exemplified in the recent works of Vogl [7], Mana and Rienitz [10], we also consider the question of how we can better measure the isotope ratios by enabling the possibility to perform matrix matching. In a way, matrix-matching isotope dilution is an extension of matching the measured isotope ratios [11] which is known to improve the quality of IDMS results. Here we introduce the concept of exact-matching of sample composition which can be achieved by means of ternary mixture analysis. Table 2 summarizes the main methods discussed in this paper.

**Table 2.** Overview of isotope dilution methods discussed in this work.

| Method | Mixtures | Other input variables |
|---|---|---|
| | *Binary mixtures* | |
| ID$^1$MS | AB | $w_B, R_B, R_A$ |
| ID$^2$MS | AB and A∗B | $w_{A*}, R_B, R_A$ |
| ID$^3$MS | AB and A∗B×2 | $w_{A*}, R_A$ |
| ID$^3$MS | AB×2 and A∗B | $w_{A*}, R_A$ |
| | *Ternary mixtures* | |
| SA-ID$^1$MS | AA∗B | $w_B, R_B, R_A$ |
| SA-ID$^2$MS | AA∗B×2 | $w_{A*}, R_B, R_A$ |
| SA-ID$^3$MS | AA∗B×3 | $w_{A*}, R_A$ |

### *3.1. Coherence of equations*

A necessary logical feature of all SA-ID$^n$MS equations is that they scale to ID$^n$MS equations under suitable experimental design. For example, SA-ID$^2$MS equation becomes ID$^2$MS equation if $m_{A,2} = 0$ and $m_{A*,1} = 0$. Additional feature of all SA-ID$^n$MS equations is that they reduce to SA-ID$^m$MS where $m < n$. Consider SA-ID$^3$MS as an example. When the third isotope ratio measurement, $R_3$, is done on a single pure component B, SA-ID$^3$MS becomes SA-ID$^2$MS. Mathematically, this corresponds to $R_3 = R_B$ and $m_{A,3} = m_{A*,3} = 0$. The SA-ID$^3$MS equation thereby reduces to SA-ID$^2$MS. Other transformations could be performed and they demonstrate the general coherence between the ternary and binary isotope dilution equations.

### *3.2. Optimal experimental designs*

The quality of results obtained by applying either the method of standard addition or isotope dilution depends on the experimental design. Thus for example, analysts know that spiking in standard addition method should be aimed to double or triple the analytical signal, as a rule of thumb [12]. Likewise, best performance in isotope dilution (ID$^1$MS) is achieved when the ratio of the blend is most dissimilar between that of the pure analyte and the pure spike. In addition, higher-order isotope dilution methods perform best when the isotopic composition of the sample/spike blend is equal to that in the standard/spike blend [11], a condition that known as the "exact matching".

The performance of SA-IDMS methods also depends on the experimental design. In this section we will explore the performance of various experimental designs of SA-IDMS methods. We shall employ the experiment design matrices where the numbers represent the relative mass of sample (A), standard (A∗) and the spike (B) in each of the mixtures subject to measurement. For example, a typical standard addition experiment with two-level additions to the sample can be described using the following design matrix:

$$E_{SA} = \left[\begin{array}{ccc} m_A & m_{A*} & m_B \\ \hline 1 & 0 & 0 \\ 1 & 1 & 0 \\ 1 & 2 & 0 \end{array}\right] \tag{11}$$

In practice, all three mixtures are diluted to equal mass or volume in order to ensure identical concentration of sample matrix.

### *3.3. SA-ID$^2$MS*

Consider SA-ID$^2$MS model with A = A∗ and with highly orthogonal isotopic patterns of A and B. For example, $x_{i,A} = x_{i,A*} = 0.95$ and $x_{i,B} = 0.05$. One experimental design that appears intuitively as "good"is:

$$E_{\text{SA-ID}^2\text{MS}} = E_1 = \left[\begin{array}{ccc} m_A & m_{A*} & m_B \\ \hline 1 & 0 & 1 \\ 1 & 1 & 2 \end{array}\right] \tag{12}$$

Here, the mass of A is kept constant between the two mixtures in order to ensure identical matrix composition, the mass of A∗ in the mixture #2 is chosen to match the mass of A in the sample, and the mass of B in each mixture is chosen to match the sum of A and A∗. Such design ensures not only matrix matching between the two mixtures but it also provides isotope ratio matching ($R_1 = R_2$ if A = A∗). Similar to this, a commonly employed design for ID$^2$MS also uses exact-matching ($R_1 = R_2$):

$$E_{\text{ID}^2\text{MS}} = E_2 = \left[\begin{array}{ccc} m_A & m_{A*} & m_B \\ \hline 1 & 0 & 1 \\ 0 & 1 & 1 \end{array}\right] \tag{13}$$

The question as to what constitutes the best experimental design can, in general, be addressed using Monte Carlo modeling of uncertainty propagation [13]. For this purpose, design matrices $E_1$ and $E_2$ were compared using $x_{i,A} = x_{i,A*} = 0.95$ and $x_{i,B} = 0.05$ with 1 % relative uncertainty on all isotope ratio measurements ($R_1$ and $R_2$). The experimental design $E_2$ (ID$^2$MS) yields 1.6 % relative uncertainty for $w_A$ whereas $E_1$ (SA-ID$^2$MS) yields 3.2 % uncertainty. This increase in uncertainty appears to be the price of switching from ID$^2$MS to SA-ID$^2$MS in order to ascertain the matrix effect. Note however, that $E_1$ does not represent the best performance of SA-ID$^2$MS and it was selected here for illustrative purposes only.

In the method of standard addition, one matches the sample matrix across all analyzed samples while varying the measured signal intensity. Likewise, in SA-ID$^2$MS one matches the sample matrix while varying

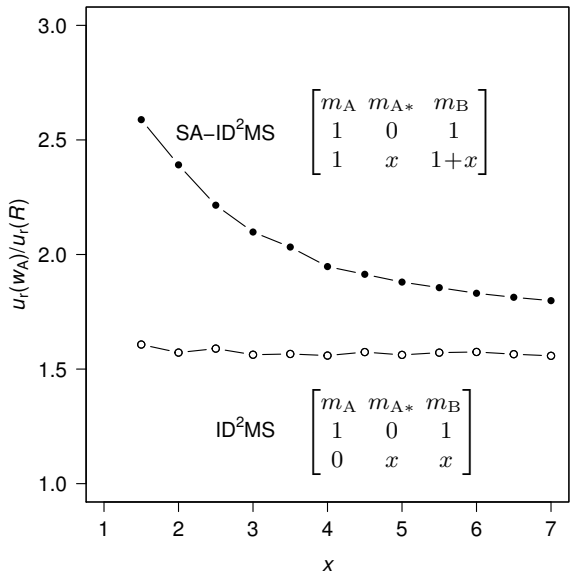


**Figure 1.** Uncertainty magnification profiles in exact-(isotope ratio)-matching SA-ID$^2$MS and ID$^2$MS as a function of the mass ratio between the added natural standard and the analyte (variable $x$, see Eq. 14). Calculations were performed using Monte Carlo simulations with 1 % relative uncertainty (Gaussian) added to isotope ratios $R_1$ and $R_2$. "3x" means that the relative uncertainty of $w_A$ is three times the relative uncertainty of $R_1$, and $R_2$. The following isotopic composition was used for A, A$*$, and B: $\{x_{i,A}, x_{i,A*}, x_{i,B}\} = \{0.95, 0.95, 0.05\}$. Each data point represents a standard deviation from $10^4$ simulations.

the measured signal intensity for each isotope. To ensure that the measured isotope ratios $R_1$ and $R_2$ remain the same (exact matching of isotope ratios), the following design matrix can be written as a function of the amount of the added primary standard (A$*$):

$$E_3 = \begin{bmatrix} m_A & m_{A*} & m_B \\ \hline 1 & 0 & 1 \\ 1 & x & 1+x \end{bmatrix} \qquad (14)$$

The performance of SA-ID$^2$MS closely reflects that of SA whereby large spiking ($x \gg 1$) will ensure, mathematically speaking, low uncertainty of the result. In practice, however, standard addition is performed in such a way that the highest measured signal intensity is approximately three to four times larger than that of the unspiked sample. If same strategy is applied to SA-ID$^2$MS, by setting $x = 2$ or 3, then the relative uncertainty of $w_A$ in SA-ID$^2$MS becomes 2.4 % or 2.1 % which is only marginally larger than 1.6 % for $E_2$. Figure 1 summarizes the comparative performance of ID$^2$MS and SA-ID$^2$MS models.

### *3.4. SA-ID$^3$MS*

The above comparison of ID$^2$MS and SA-ID$^2$MS suggests that the application of matrix-matched IDMS variant can be possible without significant error magnification. In this vein, SA-ID$^3$MS should also be feasible in practice. In order to identify useful boundaries of application, we evaluated the relative uncertainty of the design matrix for SA-ID$^3$MS:

$$E_{\text{SA-ID}^3\text{MS}} = E_4 = \begin{bmatrix} m_A & m_{A*} & m_B \\ \hline 1 & 0 & 1 \\ 1 & a_{*2} & b_2 \\ 1 & a_{*3} & b_3 \end{bmatrix} \qquad (15)$$

where four variables $a_{*2}$, $a_{*3}$, $b_2$, and $b_3$ were independently varied from $10^{-3}$ to $10^3$. For each randomly chosen design matrix $E_4$, the corresponding isotope ratios $R_1$, $R_2$, and $R_3$ were calculated (Eq. 4). All three isotope ratios were then perturbed with 1 % noise (Gaussian) in $10^3$ Monte Carlo simulations where each simulation yielded a single value of $w_A$. This simulation yields the relative uncertainty of $w_A$ as a function of the measured isotope ratios $R_1$, $R_2$, and $R_3$. Since the composition of mixture #1 remains constant, the relative uncertainty of $w_A$ can be plotted as a function of $R_2$ and $R_3$ (see Figure 2).

Several observations can be made in regards to SA-ID$^3$MS by inspecting Figure 2. First, unlike in SA-ID$^2$MS, the amount of the internal standard (B) cannot be kept constant between all three mixtures

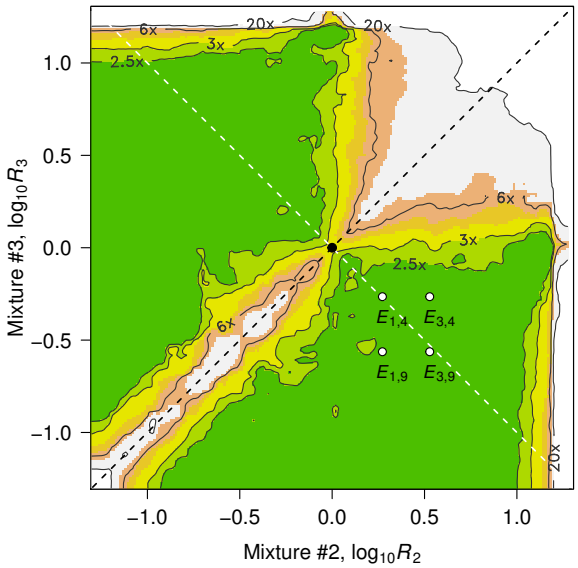


**Figure 2.** Uncertainty magnification profile for $w_A$ as a function of $R_2$ and $R_3$ in SA-ID$^3$MS (plotted using decimal logarithms of these variables, $\log_{10}R_2$ and $\log_{10}R_3$). Calculations were performed using Monte Carlo simulations with 1 % relative uncertainty (Gaussian) added to isotope ratios $R_1$, $R_2$, and $R_3$. "3x" means that the relative uncertainty of $w_A$ is three times the relative uncertainty of $R_1$, $R_2$, and $R_3$. The following isotopic composition was used for A, A$*$, and B: $\{x_{i,A}, x_{i,A*}, x_{i,B}\} = \{0.95, 0.95, 0.05\}$. The surface plot is obtained from ca. $10^5$ data points each representing standard deviation from $10^3$ simulations.

in SA-ID$^3$MS because it leads to an indeterminate condition $R_1 = R_2 = R_3$ which is the focal point of Figure 2. This focal point is at the crossroads of two opposing conditions, $R_2R_3 = R_1$ and $R_2/R_3 = R_1$, and SA-ID$^3$MS equation cannot provide a result for $w_\mathrm{A}$ at this precise condition. In addition, one can observe, broadly speaking, that the best measurement performance is achieved when isotope ratios of mixtures #2 and #3 are reciprocal to one another and when their product, $R_2R_3$, is matched to $R_1$, i.e., $R_2R_3 = R_1$. Cases corresponding to this condition lie on the dotted diagonal line in Figure 2 ($\log_{10}R_3 = 1 - \log_{10}R_2$). Note that there are many other experimental designs capable of delivering low uncertainties. For tutorial purposes, we identify the following general experimental design matrix:

$$E_{a*,b} = \left[\begin{array}{ccc} m_\mathrm{A} & m_{\mathrm{A}*} & m_\mathrm{B} \\ \hline 1 & 0 & 1 \\ 1 & a_* & 1 \\ 1 & 1 & b \end{array}\right] \qquad (16)$$

All designs within the confines of $a_* \approx 1 \ldots 7$ and $b = 2 \ldots 7$ perform well and some of them are shown in Figure 2 as $E_{a*,b}$. One such design is $E_{1,4}$ which corresponds to $\{R_1, R_2, R_3\} \approx \{1, 2, \frac{1}{2}\}$. Similar conclusions were obtained in our earlier work on ID$^4$MS where good performance was observed when the three calibration blends were selected such that $\{R_1, R_2, R_3\} \approx \{1, 2, \frac{1}{2}\}$ and the sample blend was selected such that $R_4 = 1$ [9, 14].

## 4. Conclusion

This manuscript proposes a novel approach to isotope dilution by suggesting ternary and not binary mixture analysis. This allows one to match the sample matrix between all measured solutions, similar to what is done in standard additions. Although the work presented herein outlines only the theoretical aspects of the proposed method, work is under way in our laboratory to focus on practical applications.

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