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Research note

Estimation of the uncertainty of the quantification limit

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ABSTRACT

A method to compute the standard deviation of detection and quantification limits based on an easy equation was proposed. The results were compared to those coming from the rigorously theoretical approach proposed in the literature which required quite complex computations. The results were in excellent agreement with the theoretical ones. The proposed equation represents an easy tool to establish whether an instrumental technique furnishes equivalent results in different operating conditions and to compare a limit of quantification to a law limit. The application to an experimental calibration of some elements by ICP-MS technique demonstrated its easy use for the interpretation of the results.

1. Introduction

In the last 10 years, Voigtman published a series of papers where the theory of limits of detection was deeply discussed [1–8]. The chemical measurement system was assumed to be univariate linear with an additive Gaussian white noise, either homoscedastic or heteroscedastic in character. Voigtman performed an estimation of the detection limit following the schema of Currie who invoked the type I- and type II-errors [2,8,9]. The detection limit was defined as $x_D = k\, s_{blank}/b$, where k was a "coverage factor", s_{blank} was a sample standard deviation of the blank, and b a slope of an experimental linear calibration curve. The k value was a product of the sum of the critical t values for false positive and false negative probabilities and of a "blank-subtraction" factor, which involved the use of the experimental linear regression intercept. Further, Voigtman demonstrated that the detection limit in the content domain is distributed as a *modified* non-central *t* distribution (MNC*t*D) that offered the way for the estimation of its precision in terms of standard deviation or of confidence interval [2,3]. The quantification limit is traditionally defined as 3 times the detection limit and therefore is also distributed as a MNC*t*D [10]. This important finding is crucial for comparing either the quantification limit of an analytical method to the law limit or the quantification limits obtained with a given technique in different operating conditions. However, the obtainment of the confidence interval, or of the standard deviation, of the limits from the MNC*t*D is quite cumbersome since it needs a numerical integration [2].

In this note a simple formula to estimate the standard deviation of the detection limit $x_D = k\, s_{blank}/b$ and then of the quantification limit $x_Q = 3x_D$, will be proposed. The comparison between theoretical and approximated values of the standard deviation will be tested in a real case relative to the determination of some metals with the ICP-MS technique. In particular, three representative elements will be chosen (manganese, arsenic and uranium) and analyzed by using the collision cell of the ICP-MS in "no gas" and in "He" modes. The element choice was based on the fact that ^{75}As and ^{55}Mn are usually present as impurities in the ultrapure nitric acid used as solvent. Moreover, they are affected by isobaric interferences ($^{40}Ar^{35}Cl^+$, $^{59}Co^{16}O^+$, $^{36}Ar^{38}Ar^{1}H^+$, $^{38}Ar^{37}Cl^+$, $^{36}Ar^{39}K^+$, $^{43}Ar^{16}O_2^+$ for ^{75}As and $^{40}Ar^{14}N^{1}H^+$, $^{39}K^{16}O^+$, $^{37}Co^{18}O^+$, $^{40}Ar^{15}N^+$, $^{38}Ar^{17}O^+$, $^{36}Ar^{18}O^{1}H^+$, $^{38}Ar^{16}O^{1}H^+$, $^{37}Cl^{17}O^{1}H^+$, for ^{55}Mn) which require the He collision to be eliminated. On the other hand ^{238}U is virtually absent in the nitric acid and has negligible interferences. All these circumstances alter the ICP calibration requirements and therefore affect the detection and quantification limits.

2. Theoretical

2.1. Definition of the detection limit

As described in considerable detail in Voigtman's paper [2], the detection limit is defined as

$$x_D = \left(t_p + t_q\right)\eta^{1/2} s_0/b \tag{1}$$

where t_p and t_q are the critical t values for $p =$ false positive probability, $q =$ false negative probability, and for ν degrees of freedom, s_0 is the

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sample standard deviation of the noise, b is the linear regression slope of the calibration curve $y = \alpha + \beta x$. The parameter η is given by

$$\eta = \frac{1}{M} + \frac{1}{N} + \frac{\bar{x}^2}{S_{xx}} \tag{2}$$

where M is the number of replicate measurements of the n standards and of future independent replicate measurements of an analytical blank, $N = nM$ is the number of measurements for the calibration, $\bar{x} = \frac{1}{N}\sum_{i=1}^{N} x_i$ and $S_{xx} = \sum_{i=1}^{N} (x_i - \bar{x})^2$. Henceforth the sample standard error about regression is used as s_0 and therefore the number of degrees of freedom ν is $N - 2$.

2.2. Uncertainty of the detection and quantification limits

As well elucidated by Voigtman [2,3], the detection limit in Eq. (1) is a *modified* non-central t distributed random variate with probability density function given by

$$x_D \sim \frac{A\,{S_{xx}}^{1/2}}{x_D^2} t_\nu\left(\frac{A\,{S_{xx}}^{1/2}}{x_D};\delta\right) \tag{3}$$

where $A = (t_p + t_q)\eta^{1/2}$, $\delta = \beta/\sigma_b$ is the non-centrality parameter of the non-central-t distribution with ν degrees of freedom inherent to the estimate ${s_0}^2$ and σ_b is estimated by $\hat{\sigma}_b = s_0/S_{xx}^{1/2}$. The determination of the standard deviation of the detection limit using Eq. (3) requires a numerical integration that makes its use quite difficult in practice.

An alternative, more practicable, approach to the estimation of the standard deviation of the detection limit, s_{x_D}, combines the uncertainties on the variates s_0 and b. Differentiating Eq. (1), rewritten as $x_D = (t_p + t_q)\eta^{1/2}\sqrt{s_0^2}/b$, and squaring the obtained equation, the standard deviation may be expressed as:

$$s_{xD} = \left(t_p + t_q\right)\eta^{1/2}/b\left[\frac{\hat{\mathrm{var}}\left(s_0^2\right)}{4s_0^2} + s_0^2\frac{\hat{\mathrm{var}}(b)}{b^2}\right]^{1/2} \tag{4}$$

where $\hat{\mathrm{var}}(u)$ stands for the estimated variance of u [11]. Being s_0^2 a scaled χ^2 distributed variate, the estimate of the variance of s_0^2 is $\hat{\mathrm{var}}\left(s_0^2\right) = 2s_0^4/(N-2)$ [12]. Since $\hat{\mathrm{var}}(b) = s_0^2/S_{xx}$, Eq. (4) becomes

$$s_{xD} = \left(t_p + t_q\right)\eta^{1/2}s_0/b\left[\frac{1}{2(N-2)} + \frac{s_0^2}{b^2 S_{xx}}\right]^{1/2}. \tag{5}$$

Finally, the standard deviation of the quantification limit is given by

$$s_{xQ} = 3\left(t_p + t_q\right)\eta^{1/2}s_0/b\left[\frac{1}{2(N-2)} + \frac{s_0^2}{b^2 S_{xx}}\right]^{1/2}. \tag{6}$$

The relative percent error is given by

$$CV\% = 100 s_{x_Q}/x_Q = 100\left[\frac{1}{2(N-2)} + \frac{s_0^2}{b^2 S_{xx}}\right]^{1/2}. \tag{7}$$

This parameter is independent of type I- and type II-errors and depends only on the experimental design and on regression parameters.

3. Experimental

3.1. ICP-MS chemicals and procedure

All reagents were of analytical grade and were used as purchased: HNO_3 (CAS Number 7697-37-2) al 70%, purified by redistillation, ≥99.999% (Sigma Aldrich). As, Mn and U (10 mg L^{-1}) were present in the multi-element calibration standard-2A (Agilent 8500-6940). All solutions were prepared in milliQ Ultrapure water obtained with a Millipore Plus System (Milan, Italy, resistivity 18.2 MΩ cm^{-1}). The ICP-MS was tuned daily using a 1 μg L^{-1} tuning solution containing ^{140}Ce, ^{7}Li, ^{205}Tl and ^{89}Y (Agilent Technologies, UK). A 100 μg/L solution of ^{45}Sc, ^{72}Ge and ^{209}Bi (Aristar®, BDH, UK) prepared in 2% (v/v) nitric acid was used as an internal standard through addition to the sample solution via a T-junction.

3.2. Solution setup

Multielement standard solutions were prepared in 2%v/v HNO_3. The calibration solutions were prepared by gravimetric serial dilution from multi-element standard solutions, at five different concentrations. To check for instrumental drift, one of the multi-element standards was analyzed for every 10 samples. The internal standard concentration of ^{45}Sc, ^{72}Ge and ^{209}Bi was 100 μg L^{-1} in all samples and blanks.

3.3. ICP-MS system

All the elements were measured by using an inductively coupled plasma coupled to a mass spectrometer (ICP-MS) Agilent Technologies 7700x ICP-MS system (Agilent Technologies International Japan, Ltd., Tokyo, Japan). The ICP-MS was equipped with an octopole collision cell operating in kinetic energy discrimination mode. It was used for the removal of polyatomic and argon-based interferences. The instrument was optimized daily to achieve optimum sensitivity and stability according to the manufacturer's recommendations. Typical operating conditions and data acquisition parameters are summarized in Table 1.

4. Results and discussion

Fig. 1 shows the calibrations of the three elements, obtained with the two calibration modes, "no gas" and "He". The number of replicate measurements was M = 9 for each of the n = 5 standards. All calibration data sets were homoscedastic as checked by the Hartley F_{max}-test (5% significance level) [13]. In the "no gas" mode regression, large positive

Table 1
Instrumental operative conditions for ICP-MS.

Instrumental	Agilent 7700x ICP-MS
RF power	1550 W
RF matching	1.8 V
Plasma gas flow rate	15 l min^{-1} Ar
Auxiliary gas flow rate	1.0 l min^{-1} Ar
Carrier gas flow rate	1.05 l min^{-1} Ar
Make-up gas flow rate	0.0 l min^{-1} Ar
He gas flow	4.3 ml/min
CeO+/Ce+	0.90%
Ratio(2+) 70/140	0.94%
Nebulizer	Microflow PFA nebulizer
Spray chamber	Scott double-pass type at 2 °C
Torch	Quartz glass torch
Sample uptake rate	0.1 ml min^{-1}
Sample cone Nickel	1.0 mm aperture i.d.
Skimmer cone nickel	0.5 mm aperture i.d.
Sampling depth	8.5 mm
Detector mode	Dual (pulse and analog counting)
Dwell time/mass	100 ms