



Limits of quantitation – Yet another suggestion

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ABSTRACT

The work presented herein suggests that the limit of quantitation concept may be rendered substantially less ambiguous and ultimately more useful as a figure of merit by basing it upon the significant figure and relative measurement error ideas due to Coleman, Auses and Gram, coupled with the correct instantiation of Currie's detection limit methodology. Simple theoretical results are presented for a linear, univariate chemical measurement system with homoscedastic Gaussian noise, and these are tested against both Monte Carlo computer simulations and laser-excited molecular fluorescence experimental results. Good agreement among experiment, theory and simulation is obtained and an easy extension to linearly heteroscedastic Gaussian noise is also outlined.

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1. Introduction

Limits of quantitation have always been overshadowed by decision levels and detection limits. The decision level is simply the level above which it is highly improbable to find a true net blank response, while, following Currie [1], the detection limit is such that analyte present at the detection limit is highly unlikely to go undetected. But the quantitation limit is far less well formed as a concept. Currie's "10 σ " definition of it was simple, but has no fundamental justification: he simply referenced Adams et al. [2] as a reasonable source of the factor of 10. Likewise, the 1980 publication from the ACS Committee on Environmental Improvement simply defines the factor as 10 [3, p. 2247].

In 1970, Kaiser [4] provided a plausible justification of the factor based on Tschebyscheff's inequality, but that highly conservative bounding inequality is essentially a "last resort": it applies even when nothing at all is known of the distribution of the noise. With exceptions, analysts nowadays usually have some knowledge of the relevant noise distribution, thereby enabling more efficient and effective use of experimental data. Furthermore, the rise of nonparametric methodologies, such as that of the receiver operating characteristic [5], has also mitigated against the coupled use of efficient methods with Tschebyscheff's inequality.

Not surprisingly, numerous other definitions of the limit of quantitation (LOQ) have arisen since 1980 and find continued publication popularity. Mermet's thorough and cogent 2008 survey of LOQ definitions, methodologies and usages in atomic spectrometry revealed a remarkably complicated situation, with no less than 5 distinct varieties of LOQ [6]. Although Mermet provided a helpful comparison of the relative

advantages and disadvantages of the surveyed LOQ methodologies, he concluded that [6] "any LOQ can be selected, provided that both selection and procedure are clearly justified in relation to the analytical needs defined for method validation. Analytical chemistry is a science of rigor, and there is no reason why LOQ, which is a crucial characteristic of an analytical method, should escape from this rigor." Yet apparently it has escaped: in the absence of an explicitly stated, compelling, *a priori* reason for the use of an LOQ in general, analysts have free rein to construct new LOQ definitions or alter existing ones. This seriously undermines the utility and validity of LOQs as figures of merit, especially given the difficulty in interconverting results obtained with the various LOQ methodologies. Indeed, Mermet et al. [7] have since provided a detailed study of yet another possibility for quantifying LOQs: the "accuracy profile" method. At the very least, this indicates that none of the previously surveyed LOQ methodologies [6] are obviously superior.

At the risk of adding yet another variant LOQ definition to the current collection, one possible route to standardization of the LOQ is to employ a prescient idea put forth by Coleman, Auses and Gram in 1997 [8, p. 78]: the LOQ "is the lowest concentration at or above which ... measurements have at least 1.0 significant digit (at high confidence), and, equivalently, have limited relative measurement error, $RME \leq 5\%$." This, then, may constitute the fundamental reason for the formulation and usage of the LOQ concept, regardless of the specifics of any particular LOQ methodology. Clearly, if existing LOQ formalisms were brought into compliance with this requirement, it would facilitate meaningful comparisons of LOQs and promote their use as figures of merit.

Coleman et al. provided a detailed and carefully reasoned exposition of their idea, and developed it in the context of relative measurement error (RME) and fractional significant figures. However, they also used the disadvantageous Hubaux and Vos detection limit methodology [9] to find a relationship between their LOQ definition and the Hubaux

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and Vos detection limit. Subsequently, Voigtman demonstrated, in a series of publications [10–16], the optimum implementation of Currie's program and it has since become clear (*vide infra*) that it is the relationship between the LOQ and the Currie decision level, not detection limit, that is of primary utility.

2. Theory

We assume the chemical measurement system is univariate and linear in chemical content, X :

$$Y = \alpha + \beta X + \text{noise} \quad (1)$$

where α is the true intercept, β is the true slope and Y is the true response. Systematic error is assumed to be zero. The noise is additive, Gaussian white noise (AGWN) on Y and is homoscedastic, *i.e.*, $\sigma(\beta X) \equiv \sigma_0$, where σ_0 is the population standard deviation of the noise on the blank. As a consequence of the noise, a single measured response, y_i , at any arbitrary value of X , is simply a random sample from a Gaussian (aka "Normal") distribution centered at $\alpha + \beta X$ and having population standard deviation σ_0 . If ideal blank subtraction is performed, to obtain the net response, then this simply means that the errorless value α is subtracted from y_i , so the net response, $y_i - \alpha$, is a random sample of a Gaussian distribution centered at βX , with population standard deviation σ_0 . The shorthand notation for this is $(y_i - \alpha) \sim N: \beta X, \sigma_0$, where " \sim " means "is distributed as".

If α is unavailable, as is typically the case, then blank subtraction may be performed by subtracting $\hat{\alpha}$, an unbiased estimate of α . Then $(y_i - \hat{\alpha}) \sim N: \beta X, \sigma_d$, where σ_d is the population standard deviation of the difference. The relationship between σ_d and σ_0 is $\sigma_d = \eta^{1/2} \sigma_0$, where the factor $\eta^{1/2}$ is of the general form:

$$\eta^{1/2} \equiv \left[\frac{1}{M} + \text{error term(s) due to } \hat{\alpha} \right]^{1/2} \quad (2)$$

with M being the number of future blank measurements. Optimally, M is defined as unity, so that $\eta^{1/2} = 1$ only if ideal blank subtraction is performed and is otherwise greater than unity.

For maximum generality, it will be assumed that non-ideal blank subtraction is performed, *i.e.*, $\hat{\alpha}$ is used for blank subtraction even if β and σ_0 are known. Therefore, a single net response at βX will be a random sample from $N: \beta X, \sigma_d$. As is well known, there is a 95% probability, over many repetitions of the process, that the net response will be in the (central) 95% confidence interval (CI) defined by $\beta X \pm z'_p \sigma_d$, where $z'_p \equiv z_{0.025} \approx 1.959964$. Following the lead of Coleman et al. [8], the absolute measurement error is arbitrarily defined as $z'_p \sigma_d$, *i.e.*, the half-width of the 95% CI, and the maximum relative measurement error, RME(X), is

$$\text{RME}(X) \equiv \frac{z'_p \sigma_d}{\beta X} \approx \frac{1.96 \sigma_d}{\beta X} \quad (3)$$

while still remaining within the 95% CI. Note that the RME is simply defined as the half-width of the confidence interval, divided by its center value. As noted above [8], in order for the LOQ to guarantee at least one significant figure, RME(X) must not exceed 0.05. Therefore, the theoretical, content domain LOQ, denoted by X_Q , is defined as that value of X such that $\text{RME}(X_Q) \equiv 0.05$. Hence

$$X_Q \equiv \frac{z'_p \sigma_d}{0.05 \beta} = 20 \frac{z'_p \sigma_d}{\beta} = 20 \frac{z'_p \eta^{1/2} \sigma_0}{\beta} \approx 39.2 \frac{\eta^{1/2} \sigma_0}{\beta} \quad (4)$$

since $\sigma_d = \eta^{1/2} \sigma_0$. However, the theoretical, content domain Currie decision level is defined as

$$X_C \equiv \frac{z_p \eta^{1/2} \sigma_0}{\beta} \quad (5)$$

where z_p is the critical z value for probability p of false positives [10]. Typically, $p \equiv 0.05$, so that $z_p = z_{0.05} \approx 1.6448536$. As a result,

$$X_Q \equiv 20 \frac{z'_p}{z_p} X_C \approx \frac{39.2}{z_p} X_C \quad (6)$$

In the theoretical, net response domain, $Y_C = \beta X_C$ and likewise $Y_Q = \beta X_Q$. Hence,

$$Y_Q \equiv 20 \frac{z'_p}{z_p} Y_C \approx \frac{39.2}{z_p} Y_C \quad (7)$$

Values of z_p are easily found using *Microsoft Excel*, *i.e.*, $z_p = -\text{NORMSINV}(p)$, or *via* standard tables.

The experimental, content domain decision level, x_C , is given by [10,11]

$$x_C \equiv \frac{t_p \eta^{1/2} s_0}{b} \quad (8)$$

where b is an experimentally determined, unbiased estimate of β , s_0 is the sample standard deviation determined with ν degrees of freedom (dof) and t_p is the critical t value for probability p of false positives and ν dof. Then the corresponding experimental, content domain LOQ, denoted by x_Q , is

$$x_Q \equiv \frac{t'_p \eta^{1/2} s_0}{0.05 b} = 20 \frac{t'_p \eta^{1/2} s_0}{b} = 20 \frac{t_{0.025} \eta^{1/2} s_0}{b} \quad (9)$$

where t'_p is the critical t value for 95% confidence (analogous to $z_{0.025} = 1.96$) with ν dof. Combining Eqs. (8) and (9) then yields

$$x_Q \equiv 20 \frac{t'_p}{t_p} x_C \quad (10)$$

with ν dof for both critical t values. In the experimental, net response domain, $y_C = b x_C$ and $y_Q = b x_Q$. Therefore

$$y_Q \equiv 20 \frac{t'_p}{t_p} y_C \quad (11)$$

Values of t_p are easily found using *Microsoft Excel*, *i.e.*, $t_p = \text{TINV}(2p, \nu)$, or *via* standard tables.

Fig. 1 collects together Eqs. (6), (7), (10) and (11), and also gives the Currie decision level expressions ("C" subscripts) and detection limit expressions ("D" subscripts) in all four detection quadrants. The critical values z_q and t_q in the detection limit expressions are for probability q of false negatives. These are correct and unbiased for all degrees of freedom, including $\nu = 1$. Note that all of the theoretical domain expressions are errorless real numbers that require population parameters (*i.e.*, true values, since systematic error is assumed to be negligible), while the expressions in quadrant 2 are χ variates and those in quadrant 4 are modified noncentral t variates [10,11].

3. Computer simulation

The theory presented above is very simple and perfectly suited to testing *via* computer simulation. Accordingly, the following ideal model parameters were used, ignoring units: $\alpha \equiv -0.05$, $\beta \equiv 3.85$, $\sigma_0 \equiv 0.03$, $p \equiv 0.05$, $z_p \approx 1.644854$, $p' \equiv 0.025$, $z'_p \equiv z_{0.025} \approx 1.959964$, $M \equiv 1$ future blank replicate, and $\hat{\alpha}$ the sample mean of $N = 7$ i.i.d. blank replicates. In this case $\eta^{1/2} \equiv [M^{-1} + N^{-1}]^{1/2} = [1 + (1/7)]^{1/2} \approx 1.069045$, so that, from Fig 1, $X_C \equiv z_p \eta^{1/2} \sigma_0 / \beta \approx 0.013702$ and $X_Q \equiv 20(z'_p / z_p) X_C \approx 0.3265386$.

Fig. 2 shows two different simulation programs designed to test the model and its theoretically predicted X_Q . The upper half of Fig 2 shows a

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