

Minimum Detectable Value and Limit of Detection in Linear Calibration with Standard Deviation Linearly Dependent on Net State Variable

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Abstract. The minimum detectable value obtained from a particular calibration is the smallest value of the net state variable, which can be detected with a probability of $1 - \beta$ as different from zero. In this work, the procedure for the computation of the critical value and the minimum detectable value was derived from the linear calibration function following the ISO concept, and compared to the limit of detection recommended to chemists by IUPAC. It is assumed that all measurements of the response variable are independent and normally distributed with standard deviation linearly dependent on the net state variable

Keywords: Linear Calibration, Critical Value, Minimum Detectable Value, Limit of Detection

1. Introduction

The minimum detectable value of the net state variable is an important characteristic of the measurement method and enables its optimization or selection. In order to characterize a measurement process, the minimum detectable value should be stated using appropriate data. In this work, the procedures for the computation of the critical value of the response variable, Y , and the minimum detectable value of the net state variable, x , are based on the following basic assumptions:

- a) The calibration function $y = f(x)$ is linear.
 - b) The measurements of the response variable of all specimens J in reference states are assumed to be independent and normally distributed, with standard deviation not constant at different values of the net state variable.
 - c) The residual standard deviation is linearly dependent on the values of the net state variable.
- It should be noted that in chemistry y is usually instrumental signal, x is concentration of the analyte, I – number of calibration standards (including zero concentration), J – number of replicate standard measurements.

2. Estimation of minimum detectable value

The following model is based on assumptions that the calibration function is linear and standard deviation linearly depends on x and is given by:

$$y_{ij} = a + bx_i + \varepsilon_{ij}, \quad i = 1, 2, \dots, I; \quad j = 1, 2, \dots, J \quad (1)$$

where

- x_i net state variable in the state i
- a, b model parameters
- y_{ij} response variable for the state i and specimen j
- ε_{ij} independent random errors normally distributed with expectation $E(\varepsilon_{ij}) = 0$ and variance $V(\varepsilon_{ij}) = \sigma^2(x_i) = (c + dx_i)^2$

The parameters of the model, a , b , c and d were estimated in two steps (see [1]). The first step comprises iterative estimation of the linear relationship between the residual standard deviation and the net state variable. It can be easily performed e.g. in MS Excel by using

Solver option from the Tools menu and setting 3 as the number of iterations. Empirically obtained standard deviations are used as the starting estimates of $\hat{\sigma}_0$. The third iteration usually gives the final result that is

$$\hat{\sigma}(x) = \hat{c}_3 + \hat{d}_3 x = \hat{\sigma}_0 + \hat{d}x \quad (2)$$

The second step includes estimation of the calibration function parameters:

$$\hat{a} = \frac{J \sum_{i=1}^I w_i x_i^2 \sum_{j=1}^J w_j \bar{y}_{ij} - J \sum_{i=1}^I w_i x_i \sum_{j=1}^J w_j x_i \bar{y}_{ij}}{J \sum_{i=1}^I w_i J \sum_{i=1}^I w_i x_i^2 - \left(J \sum_{i=1}^I w_i x_i \right)^2} \quad (3)$$

$$\hat{b} = \frac{J \sum_{i=1}^I w_i \sum_{j=1}^J w_j x_i \bar{y}_{ij} - J \sum_{i=1}^I w_i x_i \sum_{j=1}^J w_j \bar{y}_{ij}}{J \sum_{i=1}^I w_i J \sum_{i=1}^I w_i x_i^2 - \left(J \sum_{i=1}^I w_i x_i \right)^2} \quad (4)$$

where w_i denotes the i -th weight

$$w_i = \frac{1}{\hat{\sigma}^2(x_i)} = \frac{1}{(\hat{\sigma}_0 + \hat{d}x_i)^2}.$$

The critical value of the response variable is derived by expressing the variance $V(\bar{y} - \hat{a})$ between the average \bar{y} at the basic state and the estimated intercept as:

$$y_c = \hat{a} + t(\nu, 0.95) \sqrt{\hat{\sigma}_0^2 + \left(\frac{1}{J \sum_{i=1}^I w_i} + \frac{\bar{x}_w^2}{S_{xxw}} \right) \hat{\sigma}_{yxw}^2} \quad (5)$$

and the critical value of the net state variable is

$$x_c = \frac{t(\nu, 0.95)}{\hat{b}} \sqrt{\hat{\sigma}_0^2 + \left(\frac{1}{J \sum_{i=1}^I w_i} + \frac{\bar{x}_w^2}{S_{xxw}} \right) \hat{\sigma}_{yxw}^2} \quad (6)$$

where

$t(\nu, 0.95)$ - critical t -value for the number of degrees of freedom ν and quantil $(1-\alpha)$

$$\bar{x}_w = \frac{\sum_{i=1}^I w_i x_i}{\sum_{i=1}^I w_i}$$

$$S_{xxw} = J \sum_{i=1}^I w_i (x_i - \bar{x}_w)^2$$

$$\hat{\sigma}_{yxw}^2 = \frac{1}{I \cdot J - 2} \sum_{i=1}^I \sum_{j=1}^J w_i (\bar{y}_{ij} - \hat{a} - \hat{b}x_i)^2.$$

Finally, the minimum detectable value of the net state variable is given by

$$x_d = \frac{\delta(v, \alpha, \beta)}{\hat{b}} \sqrt{\hat{\sigma}^2(x_d) + \left(\frac{1}{J \sum_{i=1}^I w_i} + \frac{\bar{x}_w^2}{S_{xxw}} \right) \hat{\sigma}_{yxw}^2} \quad (7)$$

where

$\delta = \delta(v, \alpha, \beta)$ - the non-centrality parameter of the non-central t distribution [1,2]

$$v = I \cdot J - 2$$

Since $\hat{\sigma}^2(x_d)$ depends on the value of x_d yet to be calculated, x_d has to be calculated iteratively; three iterations are usually sufficient.

3. Results and Discussion

Measurement results obtained in calibration procedure used for quantitative analysis 4-amino-naphthalene-1-sulfonic acid (NSA) are summarized in Table 1. The second column contains the NSA concentrations, the third column involves the mean signal values calculated from three replicate signal measurements ($J=3$), the fourth column comprises the values of empirical standard deviation calculated from three replicates. The results of iterative calculation of the linear relationship between the residual standard deviation and NSA concentration are located in the right upper part of the table. Results of final statistical analysis are collected in the right bottom part of the table.

It happens frequently in chemical measurements that very small amounts of the component of interest are concerned. Then it is important to distinguish small concentration values from the zero concentration, given by the blank (containing all accompanying sample components except the main determined analyte). ISO 11843 standard procedures, characterizing the capability of detection by determining the critical value of the net state variable and, mainly, the minimum detectable value of the net state variable, are not widespread among the chemists who, instead of the mentioned characteristics, employ the limits of detection, LoD, in the signal (y) domain and, above all, in the concentration (x) domain. The recommendation of IUPAC for the LoD calculation [3] is relatively similar to the ISO calculation of x_c but it was hitherto given only for the homoscedastic case (constant standard deviation). The mentioned IUPAC approach [3] assumes a constant standard deviation and uses the one-sided upper confidence limit of the calibration line so that the LoD in the concentration domain is defined by

$$\text{LoD} = [t(v, 1-\alpha) \hat{\sigma}_{yx} / \hat{b}] \left[1 + 1/N + \bar{x}^2 / \sum_{n=1}^N (x_n - \bar{x})^2 \right]^{1/2} \quad (8)$$

where $\hat{\sigma}_{yx}$ means the residual standard deviation obtained in linear regression y vs. x , and $N = I \cdot J$ (I - the number of standard solutions, J - the number of parallel measurements). For the sake of better compatibility with older IUPAC LoD definitions, the value $\alpha = 0.01$ was recommended [4].

If the standard deviation is linearly proportional to concentration, the following equation can be derived, in which all used symbols are the same as defined in part 2:

Table 1. Measurement results and results of statistical analysis

i	x_i	\bar{y}_i	s_i	<i>Iterative computation of $\hat{\sigma}(x) = \hat{c}_3 + \hat{d}_3x$</i>		
1	0.022	4.26	0.39509		c	d
2	0.044	6.35	0.77019	<i>Iteration 1</i>	0.100532	13.98287
3	0.059	9.06	0.99000	<i>Iteration 2</i>	0.100532	13.98287
4	0.073	11.33	1.13530	<i>Iteration 3</i>	0.100532	13.98287
5	0.088	12.89	1.28508			
6	0.100	14.17	1.41500			
7	0.130	18.45	1.87502	<i>Results of statistical analysis</i>		
8	0.150	21.38	2.04035	$a =$	1.013391	$t(v,0.95) =$ 1.687094
9	0.160	23.21	2.42160	$b =$	137.185145	$\hat{\sigma}_0^2 =$ 0.0104346
10	0.180	26.70	2.66010	$\bar{x}_w =$	0.0514275	$\hat{\sigma}_{yxw}^2 =$ 0.8619128
11	0.240	35.20	3.63113	$S_{xxw} =$	0.0763458	$y_c =$ 1.442377
12	0.290	40.21	4.17129	$\nu =$	37	$x_c =$ 0.0031271
13	0.350	50.61	5.01099	$\alpha =$	0.05	$x_d =$ 0.0076365
				$\beta =$	0.05	LoD = 0.0045067

$$\text{LoD} = [t(v,1-\alpha) \hat{\sigma}_{yxw} / \hat{b}] \left[\frac{\hat{\sigma}_0^2}{\hat{\sigma}_{yxw}^2} + \frac{1}{J \sum_{i=1}^I w_i} + \frac{\bar{x}_w^2}{S_{xxw}} \right]^{1/2} \quad (9)$$

The LoD value calculated by weighted linear regression is in the last entry of Table 1.

4. Conclusions

Derived set of statistical equations was applied to linear calibration under assumption of standard deviation linearly proportional to the net state variable. Compared to the case with constant standard deviation the weights reflecting the variances at particular states of the net state variable and iterative solution of equations were applied. Comparison of the ISO approach and the IUPAC recommendation applied to the same chemical calibration revealed that the calculation procedures are similar and differ in the way of application of the t-distribution as well as in assumed probabilities.

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References

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