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Detection limits of chemical sensors: Applications and misapplications

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ABSTRACT

The limit of detection (LOD) and the sensitivity of a chemical sensor are defined using IUPAC guidelines. The LOD from simulated and experimental data is calculated from a calibration curve using a simple statistical model that was implemented into a spreadsheet program. This definition of the LOD is compared with the commonly used definition of the LOD, which is based on the product of sensitivity and the theoretical instrument resolution.

1. Introduction

The following instructions for "Xerox Enhanced Atomic Microscopy (XEAM)"were once posted near a departmental photocopier

- Take a photocopy of a sheet of paper at 4-fold magnification.
- Now take another photocopy of the enlarged copy – again at 4-fold magnification.
- Repeat the process 15 times for a total magnification of 1:4^{15} or 1:1.07 billion.
- At this point a 0.27 nm feature of the paper has been enlarged to fill the entire paper copy. The black smudge you see is an individual carbon atom (diameter about 0.22 nm)!

The resolving power in this XEAM experiment was calculated by assuming that one can obtain the ultimate spatial resolution (the detection limit) by extrapolation from experiments at low magnification assuming an error-free linear calibration with constant magnification (sensitivity). Many authors of articles that describe spectroscopic detection systems and chemical sensors use a similar assumption. It is quite common to find in the literature a measured sensitivity, which was obtained at high concentrations, and a calculated detection limit that may be orders of magnitude below the lowest measured value. Frequently, these detection limits are incorrectly calculated by dividing the resolution of, typically, only one of the instrumental components of the system with the sensitivity, i.e. the slope of the calibration curve. This is akin to assuming that all measurements fall almost exactly on the calibration curve and the standard deviation of the signal from the sensor is much less than the discretization-limited instrumental resolution.

Some authors have justified their approach by referring to an article on refractive index sensors by White and Fan [1], who stated – correctly, of course – that the detection limit can be obtained by dividing the sensor resolution with its sensitivity

$$x_{\mathrm{LOD}} = \frac{R}{r} \qquad (1)$$

However, the resolution, *R*, is a quantity that needs to be obtained either by repeated measurements near the suspected LOD or by statistical analysis of a calibration curve. One cannot simply assume that the sensor resolution is identical to the discretization limit of one of the components of the system. While White and Fan defined the "sensor resolution" of their particular refractive index sensor as being related to the "smallest possible spectral shift that can be accurately measured", they also stated that this is not a quantity related solely to, e.g. the spectrometer's spectral resolution, but an experimentally determined quantity that also includes, e.g. amplitude noise and temperature-induced noise. Unfortunately, the "resolution of the measurement" is a term that is used in widely different ways in optical engineering (e.g. "spectral resolution of a

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spectrometer") in physics (e.g. "vertical resolution of an oscilloscope") and in analytical chemistry, where it stands for "$t{\cdot}s_y$", i.e. the value of the Student *t*-function multiplied with the standard error of the signal, which is obtained by averaging the signal near the LOD. In this article we provide a rigorously derived but user-friendly set of equations that permit the calculation of a detection limit from a linear calibration curve. A spreadsheet program is provided in the electronic database of the journal that permits the entry of data pairs forming a calibration curve and that then calculates the LOD. It is *not* the goal of this article to provide a survey of the considerable research effort that went into statistical data analysis (see e.g. Refs. [2–5] for reviews), nor is it claimed that the analysis below will be correct for any type of data set. Some limitations of the model are given below.

Two different methods will be reviewed that may be used to calculate a limit of detection. The more commonly used method involves the repeated measurement of the sensor's response when exposed to a blank solution, i.e. one without analyte, and a solution containing the analyte at a concentration close to the LOD. The second method describes how the LOD may be obtained from a linear calibration curve. This requires the determination of confidence intervals and measurements of the sensor's response at different concentrations including some near the LOD. The second method is particularly useful when literature data need to be re-evaluated.

To illustrate the applications and limitations of both methods, the limits of detection are calculated using both simulated and experimentally obtained calibration curves.

2. Method I: determination of the limit of detection from standard deviations at low concentration

The following paragraphs provide a sketch of the accepted procedures by analytical labs and are consistent with guidelines of the *American Chemical Society* [6]. The reader is referred to analytical chemistry text books for more information on the derivations and for details on chemical quantitation. Here we follow Harris in his description of the LOD determination [7].

- We first require repeated measurements of a blank sample, i.e. one that does not contain analyte. The sensor response is repeatedly measured. The *American Chemical Society* recommends $k = 10$ of such measurements [6], but many agencies only require 7 measurements of the blank's response. The mean value, $\bar{y}_{\text{blank}}$ is obtained by averaging.
- We then prepare samples that contain analyte at a concentration about 1–5 times higher than the expected LOD and again perform k measurements at this concentration. The mean value and the standard deviation of the measurement, s_y, can be determined. Ideally the samples should be prepared independently from each other and using different stock solutions.
- The signal at the detection limit is then calculated from [8].

$$y_{\text{LOD}} = \bar{y}_{\text{blank}} + t_{\alpha,k-1} s_y \tag{2}$$

Here $\bar{y}_{\text{blank}}$ is the average signal of the k measurements of the blank samples and $t_{\alpha,k-1}$ is the α-quantile of Student's *t*-function with $k-1$ degrees of freedom where $(1-\alpha)$ designates the required confidence level. For example, if it is required that the measurement at the LOD has a 99% probability of being larger than the blank, then $\alpha = 0.02$, or $(1-\alpha) = 0.98$, owing to the two-sided nature of the *t*-distribution. When 10 samples are analyzed ($k = 10$) one obtains $t_{0.02,9} = 2.821$, whereas $t_{0.02,7} = 2.998$ for $k = 8$. A critique of Eq. (2) is given by Mocak et al. [9]. Frequently, a less stringent threshold of $(1-\alpha) = 0.95$ may be appropriate [4].

- The concentration at the detection limit can then be calculated from the sensitivity, r, i.e. the slope of the calibration curve. Assuming a linear calibration curve near the LOD, we calculate the minimum detectable concentration as

$$x_{\text{LOD}} = \frac{ts_y}{r} \tag{3}$$

Eq. (3) is identical to Eq. (1), since the sensor resolution at the LOD, is simply $t_{\alpha,k-1}$-fold larger than the measurement uncertainty, $R = ts_y$. For convenience the value of the student *t*-function is frequently assumed to be $t = 3$, but this implies that a minimum of about 16 samples (8 blanks and 8 low-concentration samples) have been analyzed. In the sensor literature it is frequently overlooked that with a single measurement near the estimated LOD it is not possible to determine the LOD, since one cannot determine the measurements' standard deviation s_y from such a single measurement.

It is important to note that the calculations above assume that the errors are normally (Gaussian) distributed, and that the error distributions of the blanks and the low-concentration measurements have an identical width.

3. Method II: determination of the limit of detection using a calibration curve

Frequently it is necessary to compare the performance of one's own sensor system to a system that has been reported previously and may not have been characterized using the above method. Assuming that the authors of the previous study provided a calibration curve, how can one estimate the LOD of their measurements?

If we were provided with n data pairs forming a linear calibration curve $\{x, y\}$, we can calculate the sensitivity as the slope of a linear fit

$$r = \frac{\Delta y}{\Delta x} = \frac{n\sum(x_i y_i) - \sum x_i \sum y_i}{D} \tag{4}$$

The signal offset, i.e. the intercept of the calibration curve, is similarly calculated as

$$b = \frac{n\sum x_i^2 \sum y_i - \sum(x_i y_i)\sum x_i}{D} \tag{5}$$

Here, the determinant in the denominator is given by

$$D = \begin{vmatrix} \sum x_i^2 & \sum x_i \\ \sum x_i & n \end{vmatrix} = n\sum x_i^2 - \left(\sum x_i\right)^2 \tag{6}$$

The standard deviations of the sensitivity and offset and their corresponding covariance (s_{rb}) are calculated from

$$s_r = s_y\sqrt{\frac{n}{D}}; \quad s_b = s_y\sqrt{\frac{\sum x_i^2}{D}}; \quad s_{rb} = -s_y^2\frac{n\bar{x}}{D} \tag{7}$$

where the average standard deviation of the sensor response is estimated from the standard error of the fit [10]

$$s_y = \sqrt{\frac{\sum(y_i - rx_i - b)^2}{n-2}} \tag{8}$$

These equations are commonly found in textbooks on analytical quantitation and are readily incorporated into a spreadsheet program. An example is provided as an electronic supplement.

Of importance in re-analysis of the previously published calibration curves is the uncertainty of the concentration measurement, s_x. Following Harris [7] we can calculate the uncertainty, s_x, at the concentration x by propagating uncertainties

$$s_x = \frac{s_y}{|r|}\sqrt{\frac{1}{k} + \frac{x^2 n}{D} + \frac{\sum x_i^2}{D} - \frac{2x\sum x_i}{D}} \tag{9}$$