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The uncertainty of a result from a linear calibration

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Abstract

The standard error of result obtained from a straight line calibration is given by a well known ISO-endorsed expression. Its derivation and use are explained and the approach is extended for any function that is linear in the coefficients, with an example of a weighted quadratic calibration in ICPAES. When calculating the standard error of an estimate, if QC data is available it is recommended to use the repeatability of the instrumental response, rather than the standard error of the regression, in the equation.

Key words:

Standard error, calibration, regression, measurement uncertainty

Introduction

Calibration of a measuring system is at the heart of many chemical measurements. It has direct relevance to the traceability of the measurement and contributes to the measurement uncertainty. A measurement can be seen as a two-step process in which an instrument is calibrated using one or more standards, followed by presentation of a sample to the instrument and the assignment of the value of the measurand. Instrumental analytical methods, particularly chromatographic, spectroscopic and electrochemical methods, are usually calibrated over a range of concentrations of the analyte. Often the calibrations are assumed (or arranged to be) linear and in the past, a graph was prepared by drawing the best straight line by eye through the points. Having obtained a response from the instrument from the sample to be analysed, the concentration of this sample was read off the graph, going from the instrument response on the y-axis to the concentration on the x-axis. While drawing a graph for the purpose of calibration is no longer done in practice, with a spreadsheet performing a least squares regression to obtain the equation of the best straight line, the calibration function is often still referred to as a 'calibration line' or 'calibration curve'.

In this paper the commonly used expression for the standard error of a result obtained from a straight line calibration is extended to a quadratic calibration, and the case where weighted regression is necessary. Spreadsheet recipes are given to accomplish these calculations.

Linear calibration by classical least squares regression

In calibration a series of x, y pairs are obtained where the response of an instrument y is obtained for a test material with measurand value x . (From now on, the x quantity will be called 'concentration', being the most common quantity measured in chemistry). A function of the form

$$Y = a + bx_i \quad (1)$$

can be fitted to the data, where the estimates of the parameters a and b , still called intercept and slope respectively, are \hat{a} and \hat{b} , and for a particular response

$$y_i = \hat{a} + \hat{b}x_i + \varepsilon_i \quad (2)$$

Classical least squares regression makes three assumptions about the system: the linear model holds for the data; errors are only in y ; these errors are normally distributed and independent of the value of x (so-called homoscedacity). If any of these assumptions is not met, then the best fit is not realised by this process. For example if there is error in x as well as y then an 'error-in-variables' model is indicated^{1,2}. If the error is proportional to concentration then a weighted least squares model should be used³. The consequences of failure of the linear model have been demonstrated by Hibbert and Mulholland⁴.

The least squares estimates of a and b can be obtained directly from the calibration data

$$\hat{b} = \frac{\sum_i \{(x_i - \bar{x})(y_i - \bar{y})\}}{\sum_i (x_i - \bar{x})^2} \quad (3)$$

$$\hat{a} = \bar{y} - \hat{b}\bar{x} \quad (4)$$

where the sum is over all data pairs, and \bar{x} and \bar{y} are the average values of x and y in the calibration set. These estimates minimise the standard error of the regression, $s_{y/x}$ (also known as the residual standard deviation)

$$s_{y/x} = \sqrt{\frac{\sum_i (y_i - \hat{y}_i)^2}{n-2}} \quad (5)$$

where \hat{y}_i is the value of y obtained from equation 2.

Having determined a calibration function the equation must be inverted to assign a concentration (\hat{x}_0) given a response (y_0) from an unknown test sample.

$$\hat{x}_0 = \frac{y_0 - a}{b} \quad (6)$$

Note that the carets on a and b will now be omitted. Equation 6 can be written in terms of the mean x and y values from the calibration, to remove the constant term a and its correlation with b when the standard error is calculated.

$$\hat{x}_0 = \frac{y_0 - \bar{y}}{b} - \bar{x} \quad (7)$$

The standard error of the estimate of the concentration from the mean of m responses, y_0 , is usually given as

$$s_{\hat{x}_0} = \frac{s_{y/x}}{b} \sqrt{\frac{1}{m} + \frac{1}{n} + \frac{(y_0 - \bar{y})^2}{b^2 \sum_{i=1}^n (x_i - \bar{x})^2}} \quad (8)$$

where there are n points in the calibration, and \bar{x} and \bar{y} are the means of the calibration data⁵. Equation 8 is quoted with a caveat that this is an approximation, which stems from the statistical difficulties of an error model applied to the inversion of equation 2^{6,7}. A rigorous derivation of the confidence interval on \hat{x}_c was given by Fieller in 1954⁸.

Derivation of the equation for the standard error of an estimated value

The derivation stems from a first-order expansion of the variance by Taylor's theorem. The procedure is straightforward and only requires knowledge of the variances, and possibly covariances, of the parameters and the ability to differentiate the equation assigning the result with respect to each parameter. For a general function

$$X = f(x_1, x_2, \dots, x_n) \quad (9)$$

$$V(X) = \left(\frac{\partial X}{\partial x_1}\right)^2 V(x_1) + \left(\frac{\partial X}{\partial x_2}\right)^2 V(x_2) + \dots + 2\left(\frac{\partial X}{\partial x_1}\right)\left(\frac{\partial X}{\partial x_2}\right)C(x_1, x_2) + 2\left(\frac{\partial X}{\partial x_1}\right)\left(\frac{\partial X}{\partial x_3}\right)C(x_1, x_3) + \dots \quad (10)$$

Equation 10 is applied to the variance of \hat{x}_c given by equation 7 with the assumptions that the variables are independent (all covariance terms are zero), and that $V(\bar{x}) = 0$, from the

base assumptions of classical least squares (all error in y). This is why we use equation 7 and not equation 6, a and b are correlated, but b and \bar{y} are not.

$$V(\hat{x}_0) = \left(\frac{\partial y}{\partial \hat{x}_0} \right)^2 V(y_0) + \left(\frac{\partial \bar{y}}{\partial \hat{x}_0} \right)^2 V(\bar{y}) + \left(\frac{\partial b}{\partial \hat{x}_0} \right)^2 V(b) \quad (11)$$

$$= \frac{V(y_0)}{b^2} + \frac{V(\bar{y})}{b^2} + \frac{V(b)}{b^2} \times \frac{(y_0 - \bar{y})^2}{b^2}$$

The variance in the response to the unknown (y_0) is usually estimated by the variance of the regression $s_{y/x}^2$. If y_0 is the mean of m independent observations then

$$V(y_0) = \frac{s_{y/x}^2}{m} \quad (12)$$

Similarly the variance of the mean of the calibration responses (\bar{y}) is

$$V(\bar{y}) = \frac{s_{y/x}^2}{n} \quad (13)$$

The variance of the slope is ⁹

$$V(b) = \frac{s_{y/x}^2}{\sum_i (x_i - \bar{x})^2} \quad (14)$$

and therefore

$$V(\hat{x}_0) = \frac{s_{y/x}^2}{b^2} \left(\frac{1}{m} + \frac{1}{n} + \frac{(y_0 - \bar{y})^2}{b^2 \sum_{i=1}^n (x_i - \bar{x})^2} \right) \quad (15)$$

which is equation 8 squared. It is seen that $V(y_0)$ is estimated by equation 12, that is from the standard error of the regression. It is possible that calibration measurements have been made under different conditions than routine measurements, for which a separate estimate of the standard deviation of the responses might well be available from in house QC measurements of repeatability. Therefore, if such data is known, then instead of equation 8, it would be clearer and better to calculate $s_{\hat{x}_c}$ as

$$s_{\hat{x}_0} = \frac{1}{b} \sqrt{\frac{s_r^2}{m} + \frac{s_{y/x}^2}{n} + \frac{s_{y/x}^2 (y_0 - \bar{y})^2}{b^2 \sum_{i=1}^n (x_i - \bar{x})^2}} \quad (16)$$

which distinguishes between the variance of the response when the instrument is presented with the sample (first term) and the component due to the lack of fit of the calibration line (second term).

Other linear calibration functions

Equations that are linear in the parameters, for example a quadratic, can be derived through equation 10. Quadratic functions are used in calibration of ICPAES and ICPMS analyses of elements with a wide range of concentrations (x), and quadratic functions

have been shown to be a better function than linear for some HPLC applications¹⁰. The observed instrumental response y (usually a number of ‘counts’ of a detector, or absorbance of a spectrophotometric detector) is

$$y = a + b_1x + b_2x^2 \quad (17)$$

As with the straight line calibration the constant, a , is eliminated by moving the origin of the calibration to the origin

$$y - \bar{y} = b_1(x - \bar{x}) + b_2(x^2 - \bar{x}^2) \quad (18)$$

In the analysis of a sample, a response (y_0) allows calculation of a concentration (\hat{x}_0)

$$\hat{x}_0 = \frac{-b_1 + \sqrt{b_1^2 - 4b_2(\bar{y} - y_0 - b_1\bar{x} - b_2\bar{x}^2)}}{2b_2} \quad (19)$$

Applying equation 10 to the variance of \hat{x}_0 from equation 19

$$V(\hat{x}_0) = \left(\frac{\partial \hat{x}_0}{\partial b_1}\right)^2 V(b_1) + \left(\frac{\partial \hat{x}_0}{\partial b_2}\right)^2 V(b_2) + \left(\frac{\partial \hat{x}_0}{\partial \bar{y}}\right)^2 V(\bar{y}) + \left(\frac{\partial \hat{x}_0}{\partial y_0}\right)^2 V(y_0) \\ + 2\left(\frac{\partial \hat{x}_0}{\partial b_1}\right)\left(\frac{\partial \hat{x}_0}{\partial b_2}\right)C(b_1, b_2) \quad (20)$$

The assumptions of the regression give $V(\bar{x}) = 0$ and $V(\bar{x}^2) = 0$, and the further assumption of independence between the indications and the parameters of the regression is made. Note that equation 19 can be differentiated and for a linear system the covariance matrix of the coefficients (b) is given by $\sigma^2 (\mathbf{x}^T \mathbf{x})^{-1}$ where σ^2 is the variance of y which can be estimated by $s_{y/x}^2$ and the matrix \mathbf{x} is the design matrix of the calibration (a column of 1's, followed by columns of the x -values and x^2 -values used in the calibration). Table 1 gives expressions for the differentials in equation 20. Kirkup and Mulholland¹⁰ have derived a similar expression but retained the constant term. In the practical implementation of their scheme, three covariance terms must be calculated ($C(a,b)$, $C(a,c)$, $C(b,c)$) in contrast to the single term in equation 20.

Table 1: Differentials in equation 20 for the calculation of the variance of an estimated value from a quadratic calibration $y - \bar{y} = b_1(x - \bar{x}) + b_2(x^2 - \bar{x}^2)$. The discriminant of the solution for x is $D = b_1^2 - 4b_2(\bar{y} - y_0 - b_1\bar{x} - b_2\bar{x}^2)$

| X in $\frac{\partial \hat{x}_0}{\partial X}$ | $\frac{\partial \hat{x}_0}{\partial X}$ |
|--|--|
| b_1 | $\frac{-1 + \frac{1}{2}D^{-1/2}(2b_1 + 4b_2\bar{x})}{2b_2}$ |
| b_2 | $\frac{b_1 - D^{1/2}}{2b_2^2} + \frac{\frac{1}{2}D^{-1/2}(4y_0 - 4\bar{y} + 4b_1\bar{x} + 8b_2\bar{x}^2)}{2b_2}$ |
| \bar{y} | $-D^{-1/2}$ |
| y_0 | $D^{-1/2}$ |

Weighted linear regression

Where a weighted regression is required the equation for the variance of the estimated concentration remains as equation 15, but the form of the covariance matrix of the coefficients and the standard error of the regression $s_{y/x}$ need to take account of the weighting matrix. There are two common situations in which data must be weighted. First if a transformation of the indications has been used to obtain a linear form ($y \rightarrow f(y)$), but the original indications have normally distributed error, the weights are

$\left(\frac{\partial f(y)}{\partial y} \right)^{-2}$. Secondly, if the data itself is heteroscedastic, with variance s_i^2 for the i th

datum, then the weighting matrix is $1/s_i^2$. If the system is both transformed and heteroscedastic then the product of the weights are applied. If \mathbf{W} is a diagonal matrix of the weights the coefficients, \mathbf{b} , are given by

$$\mathbf{b} = (\mathbf{x}^T \mathbf{W} \mathbf{x})^{-1} (\mathbf{x}^T \mathbf{W} \mathbf{y}) \quad (21)$$

The covariance matrix is

$$\mathbf{V} = (\mathbf{x}^T \mathbf{W} \mathbf{x})^{-1} (\mathbf{y}^T \mathbf{W} \mathbf{y} - \mathbf{b}^T \mathbf{x}^T \mathbf{W} \mathbf{y}) / (n - p) \quad (22)$$

with p the number of coefficients in the model and n the number of independent concentrations.

Confidence intervals

To obtain a confidence interval the standard error of the regression is multiplied by an appropriate point on the distribution function. In the case of normally-distributed data this is the two-tailed Student- t value for the degrees of freedom of the calibration ($n - 1$ or $n - 2$). The reason that at least five calibrations solutions of different concentrations should be used, is that the resulting three degrees of freedom has an associated Student's t value for $\alpha = 0.05$ of 3.18, which then multiplies $s_{\hat{x}_c}$ to give a larger confidence interval than is the case with more points. For example, ten points with eight degrees of freedom has a Student's t value of 2.30.

Example calculations

Two systems are given here to illustrate the methods described above, a linear calibration of sulfite using a channel biosensor and the weighted quadratic calibration of the ICPAES analysis of K^+ . An illustrative spreadsheet is given in the supplementary material to this paper.

Linear calibration of sulfite

The work up of data to produce a calibration graph with 95% confidence intervals on estimated values is given in Box 1 and in the spreadsheet in the supplementary material. All that is required for the calculations are the internal Excel functions LINEST, AVERAGE, SQRT and SUMSQ.

Box 1a

| | A | B | C | D | E |
|----|------|----------|----------|-------|--------|
| 1 | | DATA | | | |
| 2 | | x /mM | y/ mA | | x-<x> |
| 3 | | 0.01 | 0.0013 | | -0.267 |
| 4 | | 0.05 | 0.0350 | | -0.227 |
| 5 | | 0.1 | 0.0806 | | -0.177 |
| 6 | | 0.25 | 0.1803 | | -0.027 |
| 7 | | 0.5 | 0.3244 | | 0.223 |
| 8 | | 0.75 | 0.4852 | | 0.473 |
| 9 | mean | 0.277 | 0.1845 | sumsq | 0.428 |
| 10 | | | | | |
| 11 | | LINEST | | | |
| 12 | | b | a | | |
| 13 | | 0.641528 | 0.006990 | | |
| 14 | | 0.015976 | 0.008145 | | |
| 15 | | 0.997525 | 0.010456 | | |
| 16 | | 1612 | 4.000000 | | |
| 17 | | 0.176284 | 0.000437 | | |

Formulas shown in the image:

- $=B3-B\$9$ (for E3)
- $=SUMSQ(E3:E8)$ (for D9)
- $=LINEST(C5:C10,B5:B10,1,1)$ (for B13:C17)

Box1b

| | G | H | I | J | K | L | M | N | O |
|---|---------|----------|----------|-----------|---------|--------|--------|--------|-------|
| 1 | y0 | x0 | b term | ybar term | yo term | sx0 | 95% | x dn | xup |
| 2 | 0.00000 | -0.01090 | -0.00716 | 0.00342 | 0.0163 | 0.0181 | 0.0503 | -0.061 | 0.039 |
| 3 | 0.03000 | 0.03587 | -0.00600 | 0.00342 | 0.0163 | 0.0177 | 0.0491 | -0.013 | 0.085 |

Formulas shown in the image:

- $=(G2-\$C\$13)/\$B\13 (for H2)
- $=\$C\$15*(G2-\$C\$9)/\$B\$13^2/SQRT(\$E\$9)$ (for I2)
- $=\$C\$15/SQRT(COUNT(\$B\$3:\$B\$8)/\$B\$13)$ (for J2)
- $=\$C\$15/\$B\13 (for K2)
- $=SQRT(SUMSQ(I2:K2))$ (for L2)
- $=TINV(0.05,\$C\$16)*L2$ (for M2)
- $=H2-M2$ (for N2)

Box 1: Calculation of standard error and 95% confidence interval for an estimated concentration in a linear calibration. (a) Data and calculations for error formula including output from LINEST.(b) First rows of a calculation of the 95% confidence interval on an estimated concentration.

Quadratic calibration of ICP data

The instrumental software performs a weighted quadratic calibration on the blank subtracted data, forcing the line through zero. While this procedure can be questioned, forcing through zero leads to the following equations for the concentration (x) in terms of the coefficients (b_1, b_2) and the blank corrected response of the sample (Y)

$$Y = b_1x + b_2x^2 \quad (23)$$

$$\hat{x}_0 = \frac{-b_1 + \sqrt{b_1^2 + 4b_2y_0}}{2b_2} \quad (24)$$

The variance of the estimate is obtained from

$$V(\hat{x}_0) = \left(\frac{\partial \hat{x}_0}{\partial b_1} \right)^2 V(b_1) + \left(\frac{\partial \hat{x}_0}{\partial b_2} \right)^2 V(b_2) + \left(\frac{\partial \hat{x}_0}{\partial y_0} \right)^2 V(y_0) + 2 \left(\frac{\partial \hat{x}_0}{\partial b_1} \right) \left(\frac{\partial \hat{x}_0}{\partial b_2} \right) C(b_1, b_2) \quad (25)$$

with $V(b_1)$, $V(b_2)$ and $C(b_1, b_2)$ from the covariance matrix equation (22), and $V(y_0)$ estimated from QC or validation data, or the weights. Table 2 gives the equations of the differentials in equation 25.

Table 2: Differentials in equation 25 for the calculation of the variance of an estimated value from a quadratic calibration forced through the origin $y = b_1x + b_2x^2$. The discriminant of the function for an indication y_0 is $D = b_1^2 + 4b_2y_0$.

| X in $\frac{\partial \hat{x}_0}{\partial X}$ | $\frac{\partial \hat{x}_0}{\partial X}$ |
|--|--|
| b_1 | $\frac{-1 + D^{-1/2}b_1}{2b_2}$ |
| b_2 | $\frac{b_1 - D^{1/2}}{2b_2^2} + \frac{D^{-1/2}y_0}{b_2}$ |
| y_0 | $D^{-1/2}$ |

The regression line and 95% confidence interval of estimates of concentration are calculated in the spreadsheet shown in Box 2, and are graphed in Figure 1. The confidence intervals are quite dependent on the errors in the calibration points, but Figure 1 is typical of a number of data sets processed. The confidence intervals diverge with increasing concentration, as the contribution of the uncertainty of the quadratic term (b_2) increases (Figure 2). The effect is ameliorated by the increasing negative correlation term.

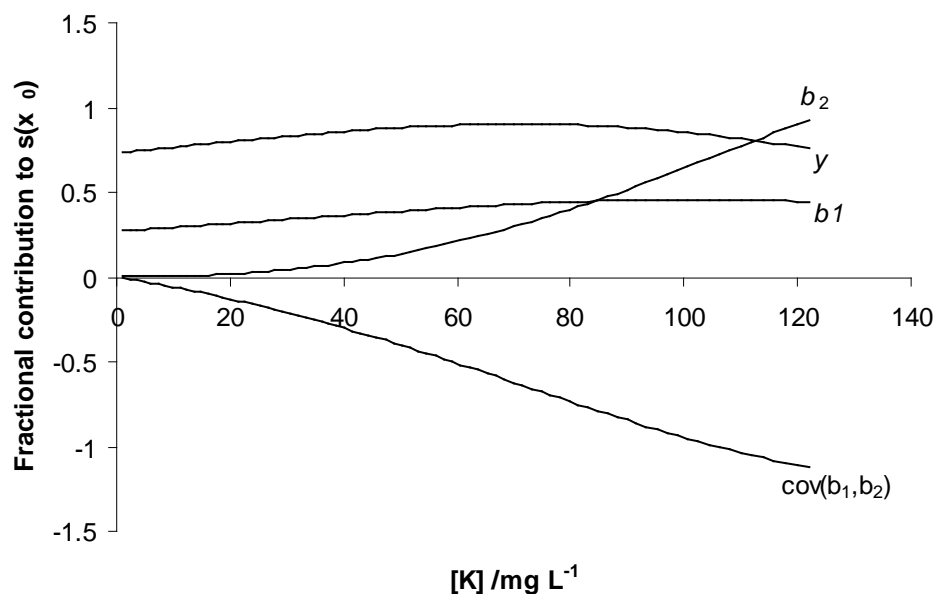


Figure 1: Calibration for the routine ICPAES analysis of potassium. Five calibration points, measured in triplicate, blank-corrected and fitted with a weighted quadratic regression through zero. Error bars are the 95% confidence interval of the mean of each point. Dashed lines are the 95% confidence interval on estimated concentrations from the calibration.

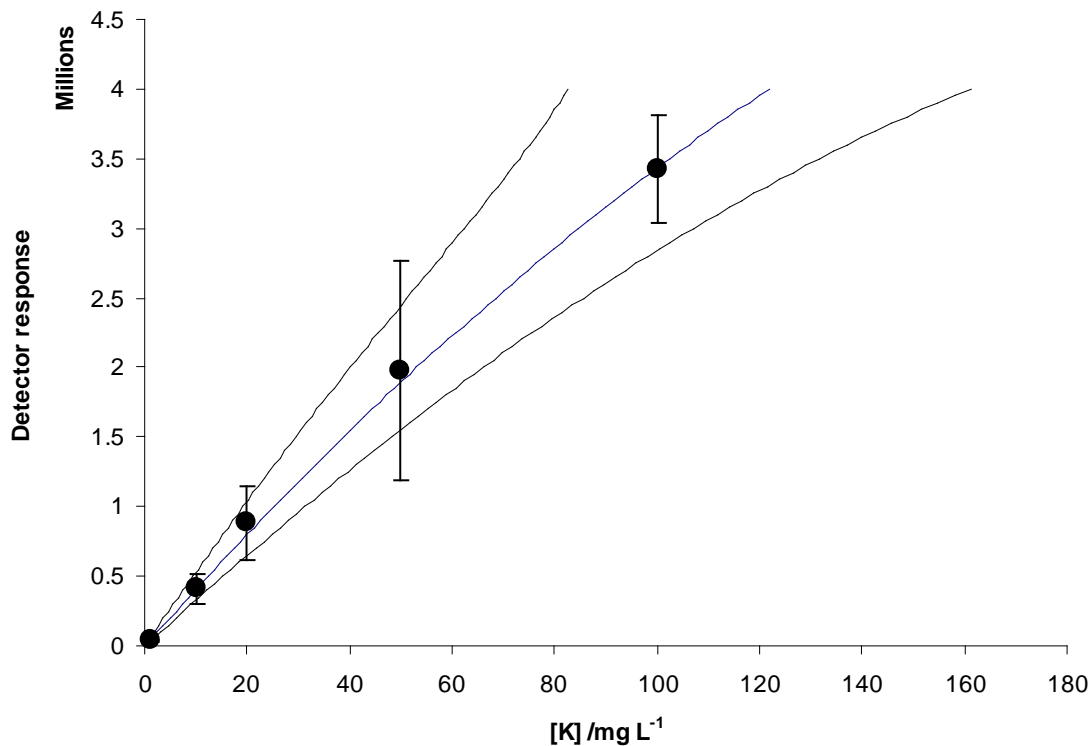


Figure 2: The fractional contributions of the components in the calibration function to the standard error of the estimates in Figure 1.

Box 2a

| | A | B | C | D | E | F | G | H | I |
|---|------------------|---|------------|---------|---------|----------------|--------|-----------------|--------|
| 1 | Blank correction | 313 | ICP output | | | | | Y | |
| 2 | [K] (mg/L) | [K] ² (mg/L) ² | r1 | r2 | r3 | mean (mg/L) | s | Blank corrected | RSD |
| 3 | 1 | 1 | 37634 | 41803 | 38257 | 39231 | 2249 | 38918 | 0.0578 |
| 4 | 10 | 100 | 431812 | 415379 | 381584 | 409592 | 25609 | 409278 | 0.0626 |
| 5 | 20 | 400 | 947664 | 825732 | 876093 | 883163 | 61273 | 882850 | 0.0694 |
| 6 | 50 | 2500 | 1779387 | 2017715 | 2138125 | 1978409 | 182570 | 1978096 | 0.0923 |
| 7 | 100 | 10000 | 3440185 | 3323442 | 3501113 | 3421580 | 90285 | 3421267 | 0.0264 |
| 8 | | | | | | | | Pooled RSD | 0.0652 |

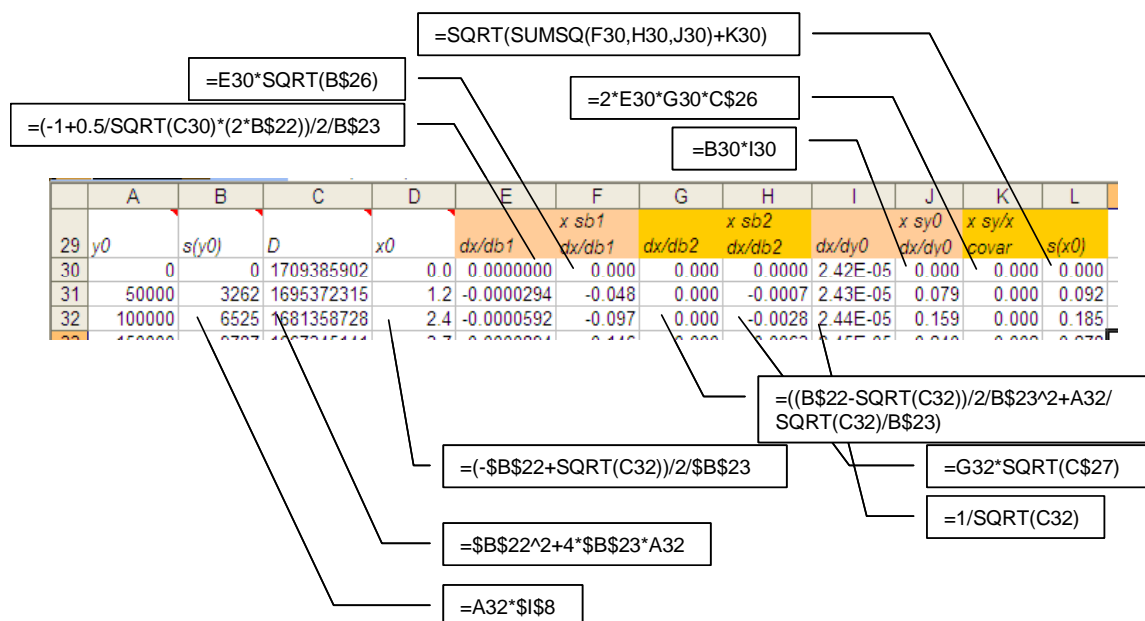
=AVERAGE(C7:E7)
 =STDEV(C7:E7)
 =F7-\$B\$1
 =SQRT(SUMSQ(I3:I7)/5)

Box 2b

| | A | B | C | D | E | F |
|----|---------------------------------|----------|----------|----------|----------|----------|
| 11 | xT | 1 | 10 | 20 | 50 | 100 |
| 12 | | 1 | 100 | 400 | 2500 | 10000 |
| 13 | yT | 38918 | 409278 | 882850 | 1978096 | 3421267 |
| 14 | | | | | | |
| 15 | W | 1.98E-07 | 0 | 0 | 0 | 0 |
| 16 | | 0 | 1.52E-09 | 0 | 0 | 0 |
| 17 | | 0 | 0 | 2.66E-10 | 0 | 0 |
| 18 | | 0 | 0 | 0 | 3.00E-11 | 0 |
| 19 | | 0 | 0 | 0 | 0 | 1.23E-10 |
| 20 | | | | | | |
| 21 | Coefficients of quadratic model | | | | | |
| 22 | b | 41344.7 | | bT | 41344.7 | -70.1 |
| 23 | | -70.1 | | | | |
| 24 | | | | | | |
| 25 | | b1 | b2 | | s(b1) | s(b2) |
| 26 | Var-covar | 2677586 | -27877 | | 1636.33 | |
| 27 | matrix | -27877 | 376 | | | 19.40 |

=1/\$G7^2
 =SQRT(B26)
 =MMULT(MINVERSE(MMULT(B11:F12,MMULT(B15:F19,A3:B7))),MMULT(B11:F12,MMULT(B15:F19,H3:H7)))
 =MINVERSE(MMULT(B11:F12,MMULT(B15:F19,A3:B7)))*(MMULT(B13:F13,MMULT(B15:F19,H3:H7))-MMULT(E22:F22,MMULT(B11:F12,MMULT(B15:F19,H3:H7))))/3

Box 2c



Box 2: Calculation of standard error for a concentration of potassium from an ICPAES analysis using a weighted quadratic calibration. The data is blank corrected and fitted through the origin. (a) Data and calculation of standard deviations for the weights for each point. (b) Matrix calculations for the variance/covariance matrix of the coefficients. (c) Calculation of first rows for standard error of the estimate of concentration. The 95% confidence intervals (not shown) are calculated from $s(x_0)$ as in Box 1b.

Some points to consider for calibrations

Although there has been much discussion about appropriate calibration methods and the correct incorporation of components in an estimate of measurement uncertainty, for routine methods that adopt linear calibration in a range in which there is a good fit to the linear model, the calibration is usually not a major source of uncertainty. The traditional “four nines r^2 ”, i.e. a squared correlation coefficient greater than 0.9999, invariably yields a useable function. Despite arguments about the unthinking use of r^2 ^{11, 12}, Ellison has shown that there is some utility in this statistic¹³.

Correlations between parameters of a calibration function are usually a significant component of the uncertainty and therefore can rarely be ignored. However the covariance matrix is usually available and the inverse calibration function can be differentiated. Thus the correct uncertainty of an estimate can be calculated. Correlations usually reduce the uncertainty, so not including them will lead to overestimated confidence intervals.

In the expression for the standard error of an estimate from a linear calibration (equation 8), the uncertainty of the observed response when the unknown is presented to the instrument usually has the greatest contribution. When its standard deviation is estimated by $s_{y/x}$, the standard error of the regression, it enters the equation as $s_{y/x}/(b \sqrt{m})$ where m is the number of replicate measurements. As m is usually one or two, the term is always greater than that for \bar{y} , $s_{y/x}/(b \sqrt{n})$, where n is the number of points in the regression (typically five or more). The contribution to uncertainty of the slope, b , is zero in the middle of the calibration when $(y_0 - \bar{y})$ is zero, and rarely is greater than the other terms.

As discussed above, there is likely to be knowledge of the standard deviation of the indication from QC data, and this is likely to be a better estimate than the standard error of the regression. Therefore I recommend use of equation 16 in such cases.

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