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True detection limits in an experimental linearly heteroscedastic system. Part 2

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ABSTRACT

Despite much different processing of the experimental fluorescence detection data presented in Part 1, essentially the same estimates were obtained for the true theoretical Currie decision levels (Y_C and X_C) and true Currie detection limits (Y_D and X_D). The obtained experimental values, for *5%* probability of false positives and *5%* probability of false negatives, were $Y_C = 56.0$ mV, $Y_D = 125.$ mV, $X_C = 0.132$ μg/mL and $X_D = 0.293$ μg/mL. For *5%* probability of false positives and *1%* probability of false negatives, the obtained detection limits were $Y_D = 158.$ mV and $X_D = 0.371$ μg/mL. Furthermore, by using bootstrapping methodology on the experimental data for the standards and the analytical blank, it was possible to validate previously published experimental domain expressions for the decision levels (y_C and x_C) and detection limits (y_D and x_D). This was demonstrated by testing the generated decision levels and detection limits for their performance in regard to false positives and false negatives. In every case, the obtained numbers of false negatives and false positives were as specified a priori.
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1. Introduction

In Part 1 [1], the authors demonstrated that a simple lab-constructed laser-excited molecular fluorescence detection system, designed to switch easily between homoscedastic and linearly heteroscedastic operation, gave experimental results in excellent agreement with previously published correct heteroscedastic theory and computer simulations. Moreover, with only simple processing of the data, not even involving use of weighted least squares, it was possible to estimate accurately the true theoretical Currie decision levels and detection limits for the system. The obtained values, for rhodamine 6 G tetrafluoroborate in ethanol and with 5% (each) probability of false positives and false negatives, were $Y_C = 56.1$ mV, $Y_D = 125.$ mV, $X_C = 0.132$ μg/mL and $X_D = 0.294$ μg/mL. For *5%* probability of false positives and *1%* probability of false negatives, the obtained detection limits were $Y_D = 158.$ mV and $X_D = 0.372$ μg/mL.

In the present work, the same experimental data as in Part 1 is processed quite differently, using weighted least squares (WLS), bootstrapping, blank subtraction via external sets of blank replicates and appropriate curve fitting of quantitatively accurate ten million event histograms. This alternative processing will be shown to validate the previously published experimental domain equations [2, Eqs. (33)–(39)], which were not tested in Part 1, and to yield essentially the same estimates of the true values of Y_C, Y_D, X_C, and X_D, as are reported in Part 1.

2. Theoretical

2.1. Background

The basic theory is exactly as presented in Part 1, Section 2.1, with one change: blank subtraction is implemented by making $M = 6$ new independent replicate blank measurements for each calibration curve and subtracting the resulting sample mean from new single future true blanks. Therefore, $M_0 = 1$, as in Part 1, and the relationship between σ_d, the population standard deviation of the blank-subtracted sample mean of M_0 future blank replicates, and σ_0, the population standard deviation of the blank, is simply

$$\sigma_d = \eta^{1/2}\sigma_0 \tag{1}$$

where

$$\eta^{1/2} = \left(\frac{1}{M_0} + \frac{1}{M}\right)^{1/2} = \left(\frac{1}{1} + \frac{1}{6}\right)^{1/2} = 1.08012344973464 \tag{2}$$

The number of blank replicates was chosen so that the degrees of freedom, ν, would be the same for both the WLS calibration curves based on $N = 7$ standards and the $M = 6$ independent blank replicates used for blank subtraction. Thus $\nu = 5$ since $N - 2 = \nu = M - 1$.

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2.2. Linearly heteroscedastic system equations

The relevant experimental, net response domain Currie decision level (y_C) and detection limit (y_D) have been previously given [2, Eqs. (33)–(35)]. These are repeated below as Eqs. (3)–(5):

$$y_D = y_C + t_q s_d(y_D) = t_p s_d + t_q s_d(y_D) \tag{3}$$

where

$$s_d^2 \equiv s_a^2 + s_0^2/M_0 \tag{4}$$

and

$$s_d^2(y_D) = s_a^2 + (s_0 + m y_D)^2/M_0 \tag{5}$$

In these equations, p = false positive probability, q = false negative probability, t_p and t_q are the critical t values for p and q respectively, s_0 is the sample standard deviation of the blank, s_d is the sample standard deviation of the blank-subtracted sample mean of M_0 future blank replicates and $s_d(y_D)$ is the sample standard deviation of the blank-subtracted sample mean of M_0 future analyte replicates for $y \equiv y_D \equiv b x_D$. The experimental, content domain Currie decision level (x_C) and detection limit (x_D) are always given by $x_C \equiv y_C/b$ and $x_D \equiv y_D/b$, respectively. Since s_d and s_0 are related in exactly the same way σ_d and σ_0 are related, i.e., $s_d = \eta^{1/2} s_0$, the sample standard error of the intercept (s_a) is computed as $s_a = (\eta - 1)^{1/2} s_0$ since $M_0 = 1$. Throughout the present work, it is assumed, unless stated otherwise, that $p = q = 0.05$ exactly.

Solving Eqs. (3)–(5) yields a quadratic equation in y_D, having the following solution:

$$y_D = \hat{B}^{-1}\left\{ y_C + \hat{A} + \left[\left(y_C + \hat{A} \right)^2 - y_C^2 \hat{B}\left(1 - t_q^2/t_p^2 \right) \right]^{1/2} \right\} \tag{6}$$

where $\hat{A}$ and $\hat{B}$ are convenience variates depending on m, the sample test statistic estimate of μ:

$$\hat{A} \equiv s_0 t_q^2 m/M_0 \;\&\; \hat{B} \equiv 1 - m^2 t_q^2/M_0 \tag{7}$$

These equations were previously given [2, Eqs. (36) and (37)]. For curve fitting (see Section 4.3), the average values of $\hat{A}$ and $\hat{B}$ are necessary. These are denoted by A_{ave} and B_{ave}, respectively, and are defined as

$$A_{ave} = \sigma_0 t_q^2 \mu/M_0 \;\&\; B_{ave} = 1 - \mu^2 t_q^2/M_0 \tag{8}$$

Note that these are not the same as A and B in Part 1, Eq. (8).

3. Experimental

3.1. Assumptions and data

The experimental system and protocol are as in Part 1: no additional data was collected. As noted above, the objective was to process differently the data already collected in order to calculate estimates of the true values of Y_C, Y_D, X_C, and X_D, and compare them with the results reported in Part 1. Ideally, the estimated true values should be independent of minor issues such as how blank subtraction is performed.

For convenience, Table 1 presents the heteroscedastic data given in Table 3 of Part 1, with an added column of raw weights, the sum of the raw weights for the 7 standards only and a normalizing factor (N_s). The raw weights are the reciprocals of the squares of the sample standard deviations shown to their immediate left. The WLS processing (see next section) uses normalized weights of the form $N_s \times$ raw weight so that the normalized weights sum to the number of standards [2].

Table 1
Concentrations, responses, noises, weights, sum and normalizing factor.

	Concentration	Response	Noise	Raw weight
Standard	μg/mL	V	V	V^{-2}
Blank	0	−0.009425240	0.03406081	858.3251
1	0.500	0.1694321	0.04766014	449.8113
2	1.00	0.3814888	0.06184867	276.2314
3	2.00	0.7734715	0.08649406	134.5739
4	4.00	1.619311	0.1368669	52.30366
5	6.00	2.515126	0.1883251	27.60156
6	8.00	3.399899	0.2398670	17.01751
7	10.0	4.242232	0.2980353	11.53154

sum = 969.0709
N_s = 7 / sum = 0.007223413

3.2. Bootstrapped WLS computer program

Fig. 1 shows the three fundamental sections of the bootstrapping computer program. The upper section consists of the WLS block, pre-loaded with the concentrations and raw weights given in Table 1. It automatically computes and uses the normalized weights. The seven inputs are Gaussian random number generators, each bootstrap modeling a specific standard. Thus, the generator for standard 1 has its population mean defined as *0.1694321* V and its population standard deviation is *0.04766014* V. These are the Response and Noise, respectively, for standard 1 in Table 1. The other *6* standards

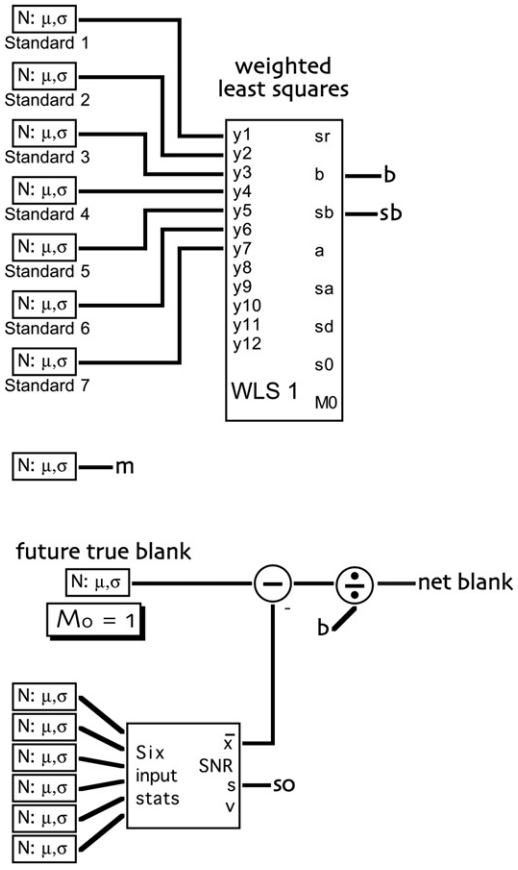

Fig. 1. Essential components of the computer program that performs weighted least squares and computes the associated statistical estimates.

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