Contents

Chapter 1

Bland-Altman Methodology

1.1   Anatomy of the Bland-Altman Plot

The issue of whether two measurement methods comparable to the extent that they can be used interchangeably with sufficient accuracy is encountered frequently in scientific research. Altman and Bland (1983) recognized the inadequacies of several analyses and articulated quite thoroughly the basis on which they are unsuitable for comparing two methods of measurement. Instead they recommended the use of graphical techniques to assess agreement. Firstly differences of measurements of two methods on the same subject should be calculated, and then the average of those measurements (Table 1.1.1). These differences and averages are then plotted (Figure 1.1.2).

In 1983 Bland and Altman published a paper in the Lancet proposing the difference plot for use for method comparison purposes (Altman and Bland, 1983). Bland-Altman plots are a powerful graphical methodology for making a visual assessment of the data. Altman and Bland (1983) express the motivation for this plot:

> "From this type of plot it is much easier to assess the magnitude of disagreement (both error and bias), spot outliers, and see whether there is any trend, for example an increase in (difference) for high values. This way of plotting the data is a very powerful way of displaying the results of a

method comparison study."

Principally their method is calculating, for each pair of corresponding two methods of measurement of some underlying quantity, with no replicate measurements, the difference d_i and mean a_i: case-wise differences of measurements of two methods $d_i = x_i - y_i$, for $i = 1, 2, \ldots, n$, on the same subject should be calculated, and then the average of those measurements, $a_i = (x_i + y_i)/2$ for $i = 1, 2, \ldots, n$. An important requirement is that the two measurement methods use the same scale of measurement. Following a technique known as the Tukey mean-difference plot, as noted by Kozak and Wnuk (2014), Altman and Bland (1983) proposed that a_i should be plotted against d_i, a plot now widely known as the Bland-Altman plot, and motivated this plot as follows:

> "From this type of plot it is much easier to assess the magnitude of disagreement (both error and bias), spot outliers, and see whether there is any trend, for example an increase in (difference) for high values. This way of plotting the data is a very powerful way of displaying the results of a method comparison study."

The case wise-averages capture several aspects of the data, such as expressing the range over which the values were taken, and assessing whether the assumptions of constant variance holds. Case-wise averages also allow the case-wise differences to be presented on a two-dimensional plot, with better data visualization qualities than a one dimensional plot. Bland and Altman (1986) cautions that it would be the difference against either measurement value instead of their average, as the difference relates to both value. This approach has proved very popular, and the Bland-Altman plots is widely regarded as powerful graphical tool for making a visual assessment of the data.

As the objective of the Bland-Altman plot is to advise on the agreement of two methods, the individual case-wise differences are also particularly relevant. The magnitude of the inter-method bias between the two methods is simply the average of the differences $\bar{d}$, and is represented with a line on the Bland-Altman plot. Further to this method, the presence of constant bias may be indicated if the average value differences

is not equal to zero. Bland and Altman (1986) do, however, state that the absence of bias does not provide sufficient information to allow a judgement as to whether or not one method can be substituted for another.

Furthermore they propose their simple methodology specifically constructed for method comparison studies. They acknowledge that there are other valid, but complex, methodologies, and argue that a simple approach is preferable to this complex approaches, *especially when the results must be explained to non-statisticians* (Altman and Bland, 1983).

1.1.1 Identity Plot

The first step recommended, which the authors argue should be mandatory, is construction of an identity plot, introduced in the last chapter as a simple scatter-plot approach of measurements for both methods on either axis, with the line of equality (the $X = Y$ line, i.e. the 45 degree line through the origin).

The line of equality should also be shown, as it is necessary to give the correct interpretation of how both methods compare. In the case of good agreement, the observations would be distributed closely along the line of equality. However, they are not useful for a thorough examination of the data. This plot can gives the analyst a cursory examination of how well the measurement methods agree. O'Brien et al. (1990) notes that data points will tend to cluster around the line of equality, obscuring interpretation. A scatter plot of the Grubbs data is shown in Figure 1.1.1. Visual inspection confirms the previous conclusion that inter-method bias is present, i.e. the Fotobalk device has a tendency to record a lower velocity.

The Bland-Altman plot for comparing the 'Fotobalk' and 'Counter' methods, which shall henceforth be referred to as the 'F vs C' comparison, is depicted in Figure 1.1.2, using data from Table 1.1.1. The dashed line in Figure 1.1.2 alludes to the inter-method bias between the two methods, as mentioned previously. Bland and Altman recommend the estimation of inter-method bias by calculating the average of the differences. In
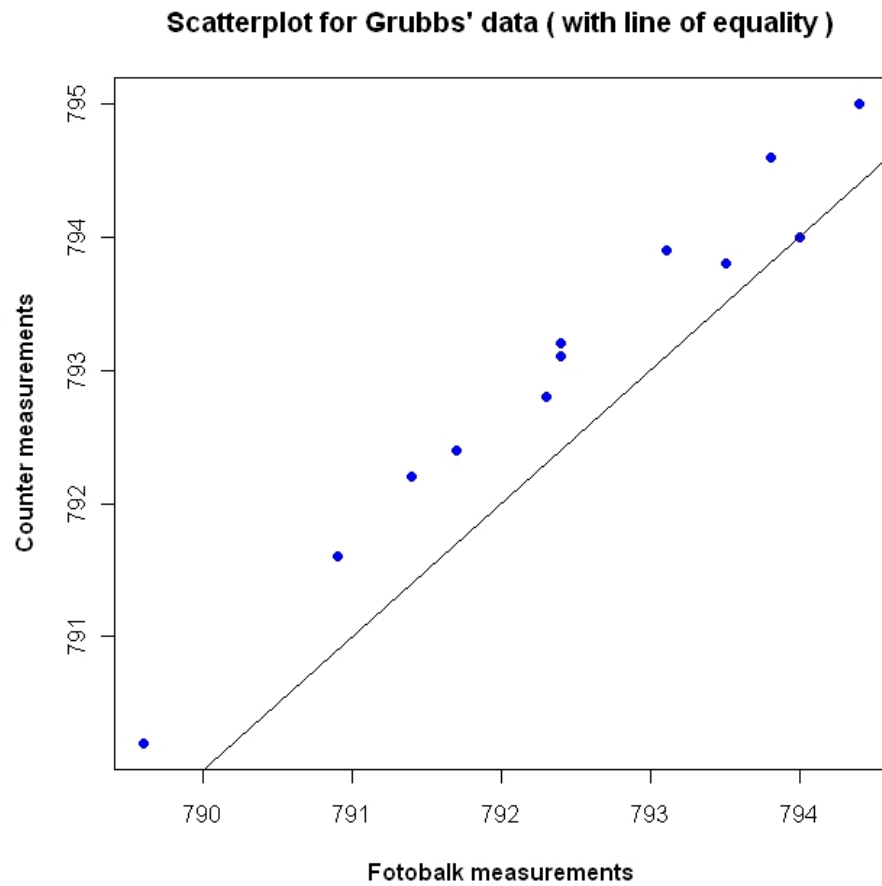
Figure 1.1.1: Scatter plot for Fotobalk and Counter methods.

the case of Grubbs data the inter-method bias is -0.6083 metres per second.

By inspection of the plot, it is also possible to compare the precision of each method. Noticeably the differences tend to increase as the averages increase.

Round	Fotobalk [F]	Counter [C]	Differences [F-C]	Averages [(F+C)/2]
1	793.8	794.6	-0.8	794.2
2	793.1	793.9	-0.8	793.5
3	792.4	793.2	-0.8	792.8
4	794.0	794.0	0.0	794.0
5	791.4	792.2	-0.8	791.8
6	792.4	793.1	-0.7	792.8
7	791.7	792.4	-0.7	792.0
8	792.3	792.8	-0.5	792.5
9	789.6	790.2	-0.6	789.9
10	794.4	795.0	-0.6	794.7
11	790.9	791.6	-0.7	791.2
12	793.5	793.8	-0.3	793.6

Table 1.1.1: Fotobalk and Counter methods: Differences and Averages.

Round	Fotobalk [F]	Terma [T]	Differences [F-T]	Averages [(F+T)/2]
1	793.8	793.2	0.6	793.5
2	793.1	793.3	-0.2	793.2
3	792.4	792.6	-0.2	792.5
4	794.0	793.8	0.2	793.9
5	791.4	791.6	-0.2	791.5
6	792.4	791.6	0.8	792.0
7	791.7	791.6	0.1	791.6
8	792.3	792.4	-0.1	792.3
9	789.6	788.5	1.1	789.0
10	794.4	794.7	-0.3	794.5
11	790.9	791.3	-0.4	791.1
12	793.5	793.5	0.0	793.5

Table 1.1.2: Fotobalk and Terma methods: Differences and Averages.

In Figure 1.3 Bland-Altman plots for the 'F vs C' and 'F vs T' comparisons are shown, where 'F vs T' refers to the comparison of the 'Fotobalk' and 'Terma' methods. Usage of the Bland-Altman plot can be demonstrate in the contrast between these comparisons. By inspection, there exists a larger inter-method bias in the 'F vs C'
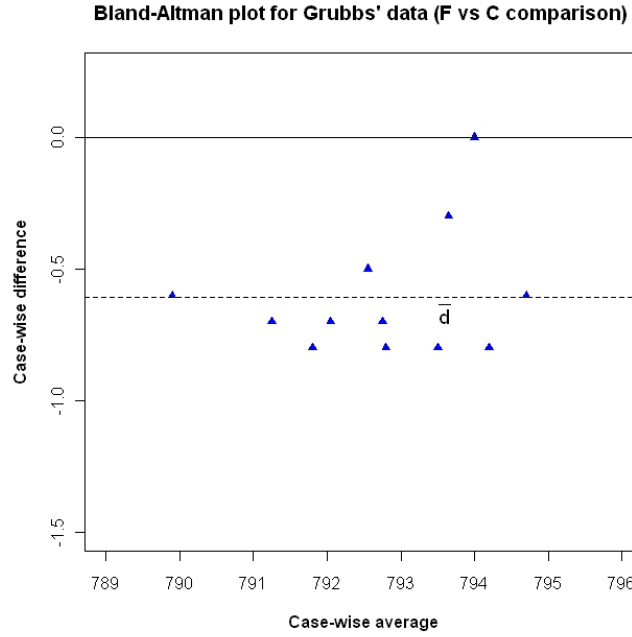
Figure 1.1.2: Bland-Altman plot For Fotobalk and Counter methods.

comparison than in the 'F vs T' comparison. Conversely there appears to be less precision in 'F vs T' comparison, as indicated by the greater dispersion of covariates.

1.1.2 Inspecting the Data

Estimates for inter-method bias and variance of differences are only meaningful if there is uniform inter-bias and variability throughout the range of measurements. Fulfilment of these assumptions can be checked by visual inspection of the plot.

Figures 1.1.4, 1.1.5 and 1.2.7 are three Bland-Altman plots derived from simulated data, each for the purpose of demonstrating how the plot would inform an analyst of trends that would adversely affect use of the recommended methodology. Figure 1.1.4 demonstrates how the Bland-Altman plot would indicate increasing variance of differences over the measurement range. Fitted regression lines, for both the upper and lower half of the plot, have been added to indicate the trend. Application of regression techniques to the Bland-Altman plot, and subsequent formal testing for the constant
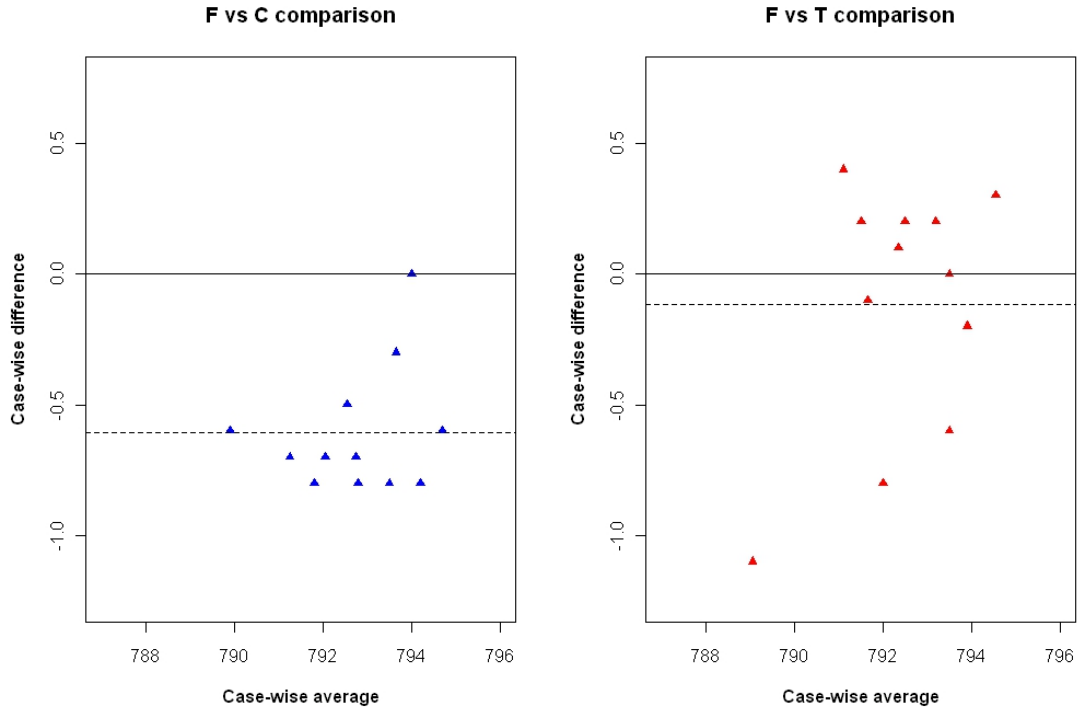
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Figure 1.1.3: Bland-Altman plots for Grubbs' F vs C and F vs T comparisons.

variability of differences is informative. The data set may be divided into two subsets, containing the observations wherein the difference values are less than and greater than the inter-method bias respectively. For both of these fits, hypothesis tests for the respective slopes can be performed. While both tests could be considered separately, multiple comparison procedures, such as the Benjamini-Hochberg (Benjamini and Hochberg, 1995) test, are advisable.

Figure 1.1.5 is an example of cases where the inter-method bias changes over the measurement range. This is known as proportional bias, and is defined by Ludbrook (1997) as meaning that 'one method gives values that are higher (or lower) than those from the other by an amount that is proportional to the level of the measured variable'. Both of these cases violate the assumptions necessary for further analysis using limits of agreement, which shall be discussed later.
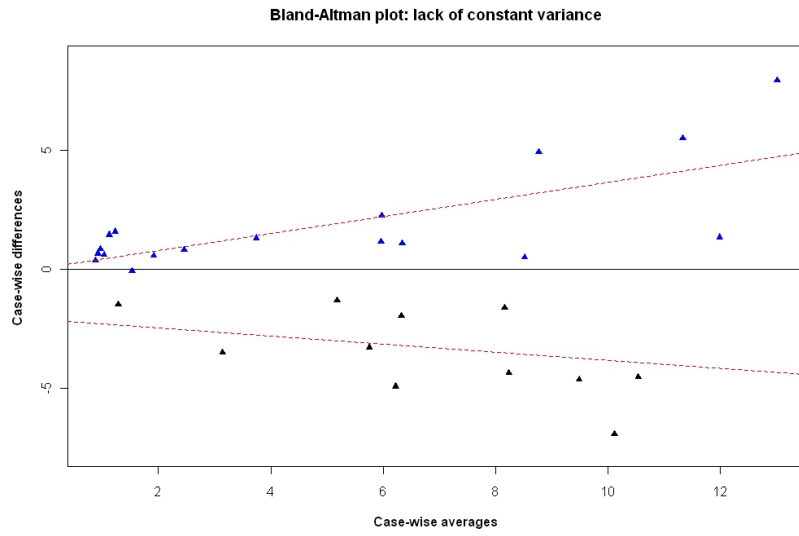
Figure 1.1.4: Bland-Altman Plot demonstrating the increase of variance over the range
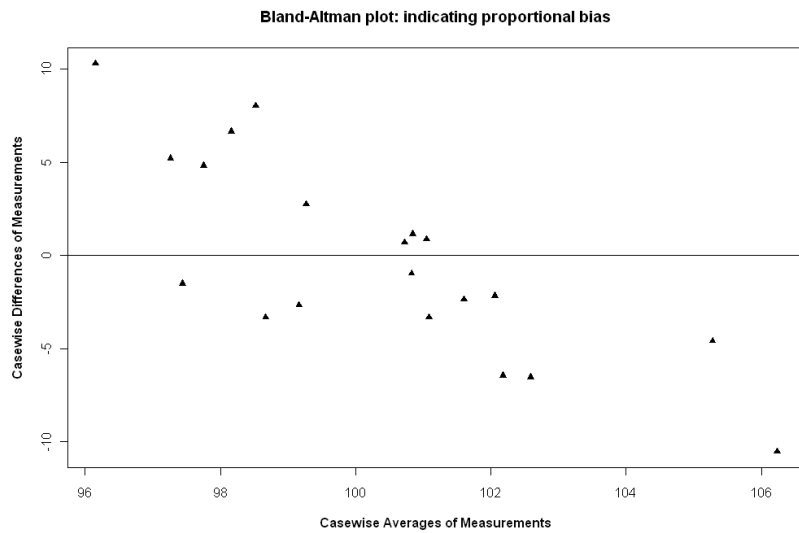

Figure 1.1.5: Bland-Altman Plot indicating the presence of proportional bias

1.1.3 Limits of Agreement

A third element of the Bland-Altman methodology, an interval known as 'limits of agreement' is introduced in Bland and Altman (1986) (sometimes referred to in liter-

ature as 95% limits of agreement). Bland and Altman proposed a pair of Limits of agreement. These limits are intended to demonstrate the range in which 95% of the sample data should lie. The Limits of agreement centre on the average difference line and are 1.96 times the standard deviation above and below the average difference line.

For the Grubbs 'F vs C' comparison, these limits of agreement are calculated as -0.132 for the upper bound, and -1.08 for the lower bound. Figure 1.1.6 shows the resultant Bland-Altman plot, with the limits of agreement shown in dotted.
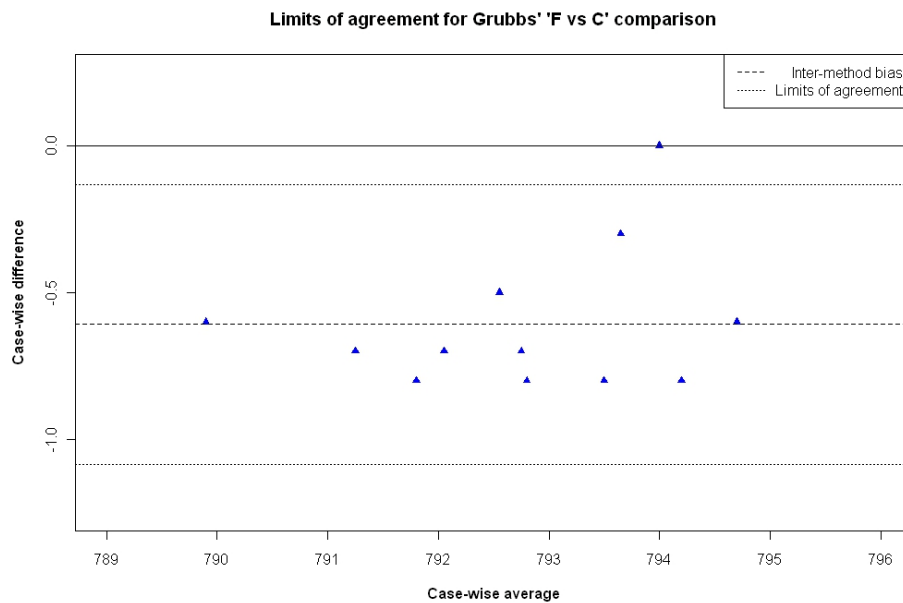
Figure 1.1.6: Bland-Altman plot with limits of agreement

Limits of agreement are used to assess whether the two methods of measurement can be used interchangeably, by demonstrating the range in which 95% of the sample data should lie. Following basic principles of the normal probability distribution, the Limits of Agreement are centred on the average difference line (which indicates the inter-method bias) and are 1.96 times the standard deviation above and below the average difference line. The limits of agreement methodology assumes a constant level of bias throughout the range of measurements.

Bland and Altman (1986) refer to this as the 'equivalence' of two measurement

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methods. The specific purpose of the limits of agreement must be established clearly. Bland and Altman (1995) comment that the limits of agreement '*how far apart measurements by the two methods were likely to be for most individuals*', a definition echoed in their 1999 paper:

> "We can then say that nearly all pairs of measurements by the two methods will be closer together than these extreme values, which we call 95% limits of agreement. These values define the range within which most differences between measurements by the two methods will lie."

The limits of agreement (LOA) are computed by the following formula:

$$LOA = \bar{d} \pm 1.96 s_d$$

with $\bar{d}$ as the estimate of the inter method bias, s_d as the standard deviation of the differences and 1.96 is the 95% quantile for the standard normal distribution.

Importantly the authors recommend prior determination of what would constitute acceptable agreement, and that sample sizes should be predetermined to give an accurate conclusion. However, Mantha et al. (2000) highlight inadequacies in the correct application of limits of agreement, resulting in contradictory estimates of limits of agreement in various papers.

1.1.4 Normality of Case-wise Differences

The difference are assumed to be normally distributed, although the measurements themselves are not assumed to follow any distribution. Therefore the authors argue that the 95% of differences are expected to lie within these limits.

Calculation of the limits of agreement relies on the assumption that the case-wise differences are normally distributed. The calculation removes a lot of the variation between subjects, leaving measurement error, which is likely to be normally distributed. Bland and Altman (1999) remark that this assumption is easy to check using a normal plot.

This assumption is justified because variation between subjects has been removed, leaving only measurement error (Bland and Altman, 1986). There are formal methodologies to test whether this assumption holds.

1.1.5   Interpretation of Limits Of Agreement

Bland and Altman (1999) note the similarity of limits of agreement to confidence intervals, but are clear that they are not the same thing. Interestingly, they describe the limits as '*being like a reference interval*', offering no elaboration.

The Shewhart chart is a well known graphical methodology used in statistical process control. Consequently there is potential for misinterpreting the limits of agreement as if they were Shewhart control limits. Importantly the parameters used to determine the limits, the mean and standard deviation, are not based on any randomly ordered sample used for an analysis, but on a statistical process's time ordered values, a key difference with Bland-Altman limits of agreement.

Carstensen et al. (2008) regards the limits of agreement as a prediction interval for the difference between future measurements with the two methods on a new individual, but states that it does not fit the formal definition of a prediction interval, since the definition does not consider the errors in estimation of the parameters.

Prediction intervals, which are often used in regression analysis, are estimates of an interval in which future observations will fall, with a certain probability, given what has already been observed. Carstensen et al. (2008) offer an alternative formulation, a 95% prediction interval for the difference

$$\bar{d} \pm t_{(0.025, n-1)} S_d \sqrt{1 + \frac{1}{n}} \qquad (1.1)$$

where n is the number of subjects. With consideration of the effect of the sample size on the interval width, Carstensen et al. (2008) remarks that only for 61 or more subjects is the quantile less than 2.

Luiz et al. (2003) describes limits of agreement as tolerance limits. A tolerance interval for a measured quantity is the interval in which a specified fraction of the

population's values lie, with a specified level of confidence. Luiz et al. (2003) offers an alternative description of limits of agreement, this time as tolerance limits.

Barnhart et al. (2007) describes them as a probability interval, and offers a clear description of how they should be used; '*if the absolute limit is less than an acceptable difference d_0, then the agreement between the two methods is deemed satisfactory*'.

Various other interpretations as to how limits of agreement should properly be defined. The prevalence of contradictory definitions of what limits of agreement strictly will inevitably attenuate the poor standard of reporting using limits of agreement, as discussed by Mantha et al. (2000).

1.1.6   Criticism of Limits of Agreement

The Bland-Altman methodology is well noted for its ease of use, and can be easily implemented with most software packages. Also it does not require the practitioner to have more than basic statistical training. The plot is quite informative about the variability of the differences over the range of measurements. For example, an inspection of the plot will indicate the 'fan effect'. They also can be used to detect the presence of an outlier.

Limits of agreement are intended to analyse equivalence. How this is assessed is the considered judgement of the practitioner. In Bland and Altman (1986) an example of good agreement is cited. For two methods of measuring 'oxygen saturation', the limits of agreement are calculated as (-2.0,2.8) percentage points. An knowledgeable practitioner would ostensibly find this to be sufficiently narrow.

If the limits of agreement are not clinically important, which is to say that the differences tend not to be substantial, the two methods may be used interchangeably. Dunn (2002) takes issue with the notion of 'equivalence', remarking that while agreement indicated equivalence, equivalence does not reflect agreement.

If one method is sometimes higher, or sometimes lower, the average of the differences will be close to zero. If it is not close to zero, this indicates that the two assay methods

are producing different results systematically.

Several problems have been highlighted regarding Limits of Agreement. One is the somewhat arbitrary manner in which they are constructed. While in essence they are similar to confidence intervals, they are not constructed as such; they are designed for future values. Ludbrook (1997, 2002) criticizes Bland-Altman plots on the basis that they present no information on effect of constant bias or proportional bias. These plots are only practicable when both methods measure in the same units, hence they are totally unsuitable for conversion problems. The limits of agreement are somewhat arbitrarily constructed. They may or may not be suitable for the data in question. It has been found that the limits given are too wide to be acceptable. There is no guidance on how to deal with outliers. Bland and Altman recognize the effect they would have on the limits of agreement, but offer no guidance on how to correct for those effects.

1.2   Detection of Outliers

The Bland-Altman plot also can be used to identify outliers. An outlier is an observation that is conspicuously different from the rest of the data that it arouses suspicion that it occurs due to a mechanism, or conditions, different to that of the rest of the observations. In their 1983 paper they merely state that the plot can be used to "spot outliers". In their 1986 paper, Bland and Altman give an example of an outlier. They state that it could be omitted in practice, but make no further comments on the matter. In Bland and Altman (1999), we get the clearest indication of what they suggest on how to react to the presence of outliers. Their recommendation is to recalculate the limits without them, in order to test the difference with the calculation where outliers are retained. Bland and Altman (1999) do not recommend excluding outliers from analyses. However recalculation of the inter-method bias estimate, and further calculations based upon that estimate, are useful for assessing the influence of outliers. Bland and Altman (1999) states that *"We usually find that this method of analysis is*

not too sensitive to one or two large outlying differences." Classification thereof is a subjective decision in any analysis, but must be informed by the logic of the formulation. Figure 1.2.7 is a Bland Altman plot with two conspicuous observations, at the extreme left and right of the plot respectively. Importantly, outlier classification must be informed by the logic of the mechanism that produces the data.
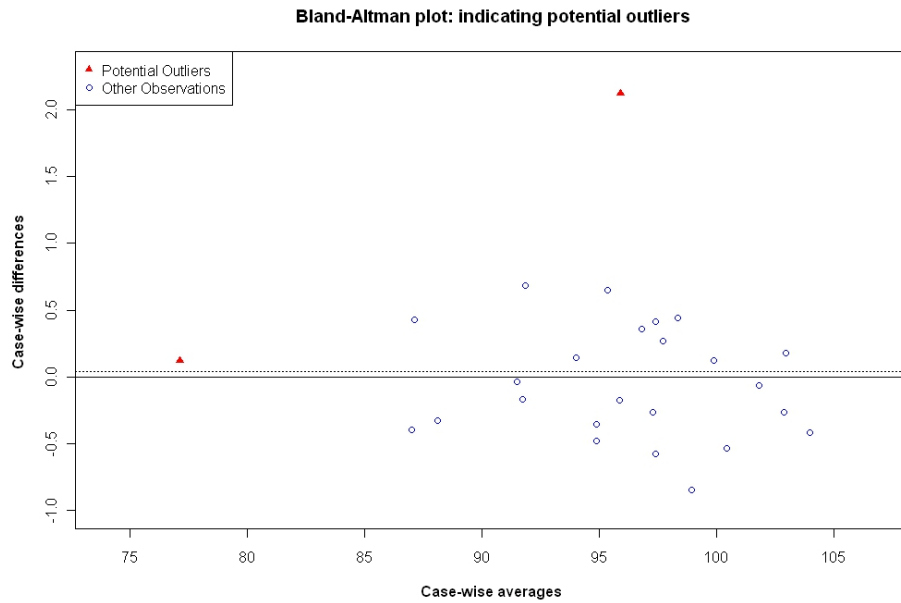

Figure 1.2.7: Bland-Altman plot indicating the presence of outliers

In the Bland-Altman plot, the horizontal displacement of any observation is supported by two independent measurements. Hence any observation, such as the one on the extreme right of figure 1.2.7, should not be considered an outlier on the basis of a noticeable horizontal displacement from the main cluster.

The one on the extreme left should be considered an outlier, as it has a noticeable vertical displacement from the rest of the observations. Conversely, the fourth observation from the original data set should be considered an outlier, as it has a noticeable vertical displacement from the rest of the observations.

1.2.1 Bartko's Ellipse

As an enhancement on the Bland Altman Plot, Bartko (1994) has expounded a confidence ellipse for the covariates. Bartko (1994) offers a graphical complement to the Bland-Altman plot in the form of a bivariate confidence ellipse as a boundary for dispersion. Altman (1978) provides the relevant calculations for the ellipse. This ellipse is intended as a visual guideline for the scatter plot, for detecting outliers and to assess the within- and between-subject variability. The stated purpose is to 'amplify dispersion', which presumably is for the purposes of outlier detection. The orientation of the the ellipse is key to interpreting the results. Additionally Bartko's ellipse provides a visual aid to determining the relationship between variances.
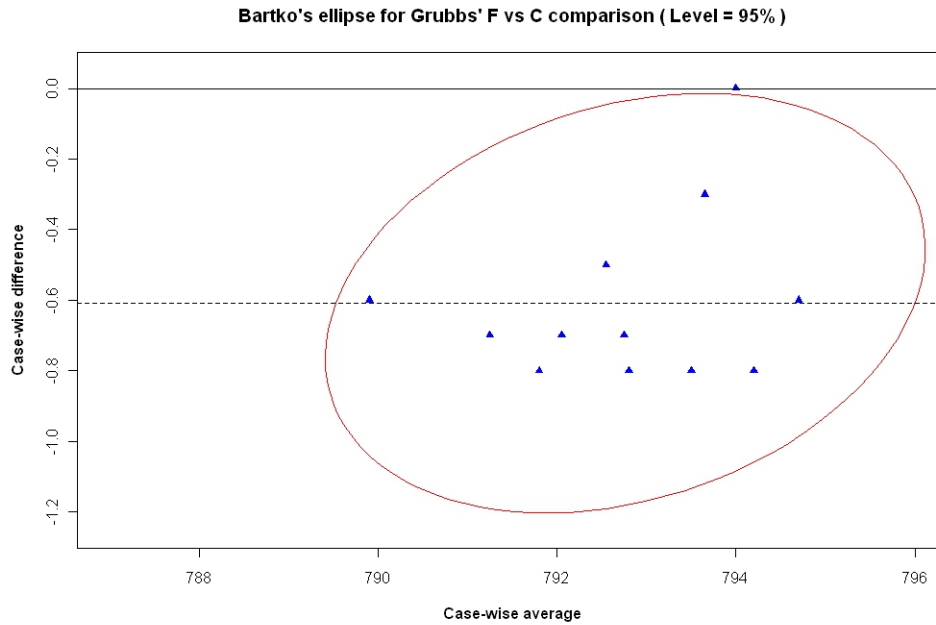

Figure 1.2.8: Bartko's ellipse for Grubbs data

The minor axis relates to the between-subject variability, whereas the major axis relates to the error mean square, with the ellipse depicting the size of both relative to each other.

Furthermore, the ellipse provides a visual aid to determining the relationship be-

tween the variance of the means var(a) and the variance of the differences var(d). If var(a) is greater than var(d), the orientation of the ellipse is horizontal. Conversely if var(a) is less than var(d), the orientation of the ellipse is vertical. The more horizontal the ellipse, the greater the degree of agreement between the two methods being tested.

Bartko states that the ellipse can, inter alia, be used to detect the presence of outliers. The limitations of using bivariate approaches to outlier detection in the Bland-Altman plot can demonstrated using Bartko's ellipse.

The Bland-Altman plot for the Grubbs data, complemented by Bartko's ellipse, is depicted in figure 1.2.8. The fourth observation is shown to be outside the bounds of the ellipse, indicating that it is a potential outlier.

A covariate is added to the 'F vs C' comparison that has a difference value equal to the inter-method bias, and an average value that markedly deviates from the rest of the average values in the comparison, i.e. 786. Figure 1.2.9 depicts a 95% confidence ellipse for this manipulated data set. By inspection of the confidence interval, we would conclude that this extra covariate is an outlier, in spite of the fact that this observation is very close to the inter-method bias as determined by this approach.

1.2.2 Grubbs' Test for Outliers

In classifying whether an observation from a univariate data set is an outlier, many formal tests are available, such as the Grubbs test for outliers. In assessing whether a covariate in a Bland-Altman plot is an outlier, this test is useful when applied to the case-wise difference values treated as a univariate data set. The null hypothesis of the Grubbs test procedure is the absence of any outliers in the data set.

The test statistic for the Grubbs test (G) is the largest absolute deviation from the sample mean divided by the standard deviation of the differences,

$$G = \max_{i=1,\ldots,n} \frac{\left| d_i - \bar{d} \right|}{S_d}. \tag{1.2}$$

For the 'F vs C' comparison it is the fourth observation that gives rise to the test statistic, $G = 3.64$. The critical value is calculated using Student's t distribution and
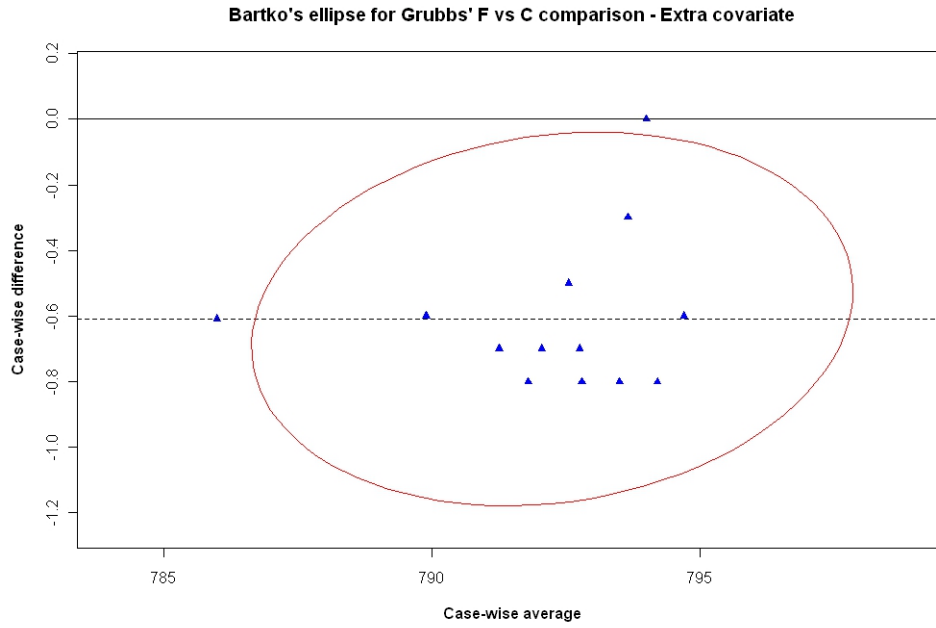
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Figure 1.2.9: Bartko's Ellipse for Grubbs' data, with an extra covariate.

the sample size,

$$U = \frac{n-1}{\sqrt{n}} \sqrt{\frac{t^2_{\alpha/(2n),n-2}}{n-2+t^2_{\alpha/(2n),n-2}}}.$$

For this test $U = 0.75$. The conclusion of this test is that the fourth observation in the 'F vs C' comparison is an outlier, with $p-$value $= 0.003$, in accordance with the previous result of Bartko's ellipse.

1.3 Precision of Limits of Agreement

The limits of agreement are estimates derived from the sample studied, and will differ from values relevant to the whole population. Bland and Altman (1986) advance a formulation for confidence intervals of the inter-method bias and the limits of agreement, arguing that it is possible to make such estimates if it is assumed that the case-wise differences approximately follow a normal distribution. However Bland and Altman (1999) caution that such calculations may be 'somewhat optimistic' if the associated

assumptions are not valid. A 95% confidence interval can be determined, by means of the t distribution with $n - 1$ degrees of freedom. For the inter-method bias, the confidence interval is simply that of a mean: $\bar{d} \pm t_{(\alpha/2,n-1)} S_d / \sqrt{n}$.

The confidence intervals and standard error for the limits of agreement follow from the variance of the limits of agreement, which is shown to be

$$\text{Var}(LOA) = \left(\frac{1}{n} + \frac{1.96^2}{2(n-1)} \right) s_d^2.$$

If n is sufficiently large this can be following approximation can be used

$$\text{Var}(LOA) \approx 1.71^2 \frac{s_d^2}{n}.$$

Consequently the standard errors of both limits can be approximated as 1.71 times the standard error of the differences.

1.4   Prevalence of the Bland-Altman plot

Bland and Altman (1986), which further develops the Bland-Altman methodology, was found to be the sixth most cited paper of all time by Ryan and Woodall (2005). Dewitte et al. (2002) reviews the use of Bland-Altman plots by examining all articles in the journal 'Clinical Chemistry' between 1995 and 2001, describing the rate at which prevalence of the Bland-Altman plot has developed in scientific literature. This study concludes that use of the Bland-Altman plot increased over the years, from 8% in 1995 to 14% in 1996, and 31-36% in 2002.

The Bland-Altman plot has since become the expected, and often the obligatory, approach for presenting method comparison studies in many scientific journals (Hollis, 1996). Furthermore O'Brien et al. (1990) recommend its use in papers pertaining to method comparison studies for the journal of the British Hypertension Society.

Mantha et al. (2000) contains a study on the use of Bland Altman plots of 44 articles in several named journals over a two year period. 42 articles used Bland Altman's limits of agreement, while the other two used correlation and regression analyses. Mantha

et al. (2000) remark that 3 papers, from 42 mention predefined maximum width for limits of agreement that would not impair medical care.

The conclusion of Mantha et al. (2000) is that there are several inadequacies and inconsistencies in the reporting of results, and that more standardization in the use of Bland Altman plots is required. The authors recommend the prior determination of limits of agreement before the study is carried out. This contention is endorsed by Lin et al. (1991), which makes a similar recommendation for the sample size, noting that *"sample sizes required either was not mentioned or no rationale for its choice was given"*.

> In order to avoid the appearance of "data dredging", both the sample size and the (limits of agreement) should be specified and justified before the actual conduct of the trial. (Lin et al., 1991)

Dewitte et al. (2002) remark that the limits of agreement should be compared to a clinically acceptable difference in measurements.

As an alternative to limits of agreement, Lin et al. (2002) proposes the use of the mean square deviation in assessing agreement. The mean square deviation is defined as the expectation of the squared differences of two readings. The MSD is usually used for the case of two measurement methods X and Y, each making one measurement for the same subject, and is given by:

$$MSDxy = E[(x - y)^2] = (\mu_x - \mu_y)^2 + (\sigma_x - \sigma_y)^2 + 2\sigma_x\sigma_y(1 - \rho_{xy}).$$

Barnhart et al. (2007) advises the use of a predetermined upper limit for the MSD value, MSD_{ul}, to define satisfactory agreement. However, a satisfactory upper limit may not be easily determinable, thus creating a drawback to this methodology.

Alternative indices, proposed by Barnhart et al. (2007), are the square root of the MSD and the expected absolute difference (EAD).

$$EAD = E(|x - y|) = \frac{\sum |x_i - y_i|}{n},$$

Both of these indices can be interpreted intuitively, since their units are the same as that of the original measurements. They can also be compared to the maximum acceptable absolute difference between two methods of measurement d_0. For the sake of brevity, the EAD will be considered solely.

The EAD can be used to supplement the inter-method bias in an initial comparison study, as the EAD is informative as a measure of dispersion, is easy to calculate and requires no distributional assumptions. A consequence of using absolute differences is that high variances would result in a higher EAD value.

	U	V	$U - V$	$|U - V|$
1	98.05	99.53	-1.49	1.49
2	99.17	96.53	2.64	2.64
3	100.31	97.55	2.75	2.75
4	100.35	96.03	4.32	4.32
5	99.51	99.00	0.51	0.51
6	98.50	100.76	-2.26	2.26
7	100.66	99.37	1.29	1.29
8	99.66	108.87	-9.21	9.21
9	99.70	105.16	-5.45	5.45
10	101.55	94.31	7.24	7.24

Table 1.4.3: Example data set

To illustrate the use of EAD, consider Table 1.4.3. The inter-method bias of 0.03, which is desirably close to zero in the context of agreement. However, an identity plot would indicate very poor agreement, as the points are noticeably distant from the line of equality.

The limits of agreement are $[-9.61, 9.68]$, which is a wide interval for this data. As with the identity plot, this would indicate lack of agreement. As with inter-method bias, an EAD value close to zero is desirable. However, from Table 1.4.3, the EAD can be computed as 3.71. The Bland-Altman plot remains a useful part of the analysis. In
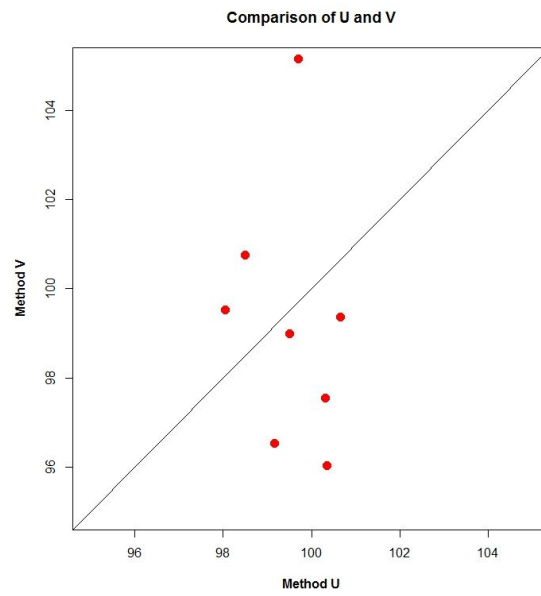
Figure 1.4.10: Identity Plot for example data

Figure 1.4.11, it is clear there is a systematic decrease in differences across the range of measurements.
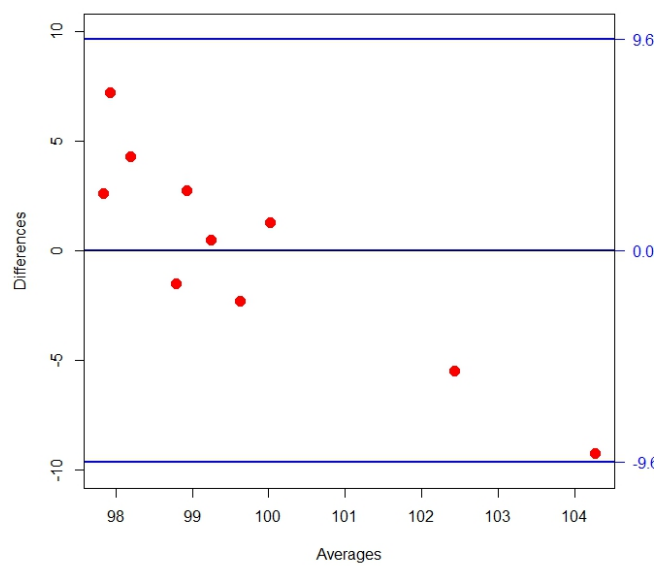

Figure 1.4.11: Bland-Altman Plot for UV comparison

Barnhart et al. (2007) remarks that a comparison of EAD and MSD, using simulation studies, would be interesting, while further adding that '*It will be of interest to investigate the benefits of these possible new unscaled agreement indices*'. For the Grubbs' 'F vs C' and 'F vs T' comparisons, the inter-method bias, difference variances, limits of agreement and EADs are shown in Table 1.5. The corresponding Bland-Altman plots for 'F vs C' and 'F vs T' comparisons were depicted previously on Figure 1.3. While the inter-method bias for the 'F vs T' comparison is smaller, the EAD penalizes the comparison for having a greater variance of differences. The EAD values for both comparisons are therefore much closer.

	F vs C	F vs T
Inter-method bias	-0.61	0.12
Difference variance	0.06	0.22
Limits of agreement	(-1.08, -0.13)	(-0.81,1.04)
EAD	0.61	0.35

Table 1.4.4: Agreement indices for Grubbs' data comparisons.

Further to Lin (2000) and Lin et al. (2002), individual agreement between two measurement methods may be assessed using the the coverage probability (CP) criteria or the total deviation index (TDI). If d_0 is predetermined as the maximum acceptable absolute difference between two methods of measurement, the probability that the absolute difference of two measures being less than d_0 can be computed. This is known as the coverage probability (CP).

$$CP = P(|x_i - y_i| \leq d_0) \tag{1.3}$$

If π_0 is set as the predetermined coverage probability, the boundary under which the proportion of absolute differences is π_0 may be determined. This boundary is known as the 'Total Deviation Index' (TDI). Hence the TDI is the $100\pi_0$ percentile of the absolute difference of paired observations.

1.5   Variations of the Bland-Altman Plot

The limits of agreement methodology assumes a constant level of bias throughout the range of measurements. As Bland and Altman (1986) point out this may not be the case. Importantly Bland and Altman (1999) makes the following point:

> These estimates are meaningful only if we can assume bias and variability
> are uniform throughout the range of measurement, assumptions which can
> be checked graphically.

The importance of this statement is that, should the Bland Altman plot indicate that these assumptions are not met, then their entire methodology, as posited thus far, is inappropriate for use in a method comparison study. Again, in the context of potential outlier in the Grubbs data (figure 1.2), this raises the question on how to correctly continue.

Due to limitations of the conventional difference plot, a series of alternative formulations for the Bland-Altman approach have been proposed. Referring to the assumption that bias and variability are constant across the range of measurements, Bland and Altman (1999) address the case where there is an increase in variability as the magnitude increases. They remark that it is possible to ignore the issue altogether, but the limits of agreement would be wider apart than necessary when just lower magnitude measurements are considered. Conversely the limits would be too narrow should only higher magnitude measurements be used.

To address the issue, they propose the logarithmic transformation of the data. The plot is then formulated as the difference of paired log values against their mean. Bland and Altman acknowledge that this is not easy to interpret, and may not be suitable in all cases.

Bland and Altman (1999) offers two variations of the Bland-Altman plot that are intended to overcome potential problems that the conventional plot would be inappropriate for. The first variation is a plot of case-wise differences as percentage of

averages, and is appropriate when there is an increase in variability of the differences as the magnitude increases.

The second variation is a plot of case-wise ratios as percentage of averages, removing the need for logarithmic transformation. This approach is useful when there is an increase in variability of the differences as the magnitude of the measurement increases. Eksborg (1981) proposed such a ratio plot, independently of Bland and Altman. Dewitte et al. (2002) commented on the reception of this article by saying '*Strange to say, this report has been overlooked*'.

1.6   Limits of Agreement for Replicate Measurements

Computing limits of agreement features prominently in many method comparison studies since the publication of Bland and Altman (1986). Bland and Altman (1999) addresses the issue of computing LOAs in the presence of replicate measurements, suggesting several computationally simple approaches. When repeated measures data are available, it is desirable to use all the data to compare the two methods. However, the original Bland-Altman method was developed for two sets of measurements done on one occasion, and so this approach is not suitable for replicate measures data. However, as a naive analysis, it may be used to explore the data because of the simplicity of the method. In addition to Bland and Altman (1999), Carstensen et al. (2008) computes the limits of agreement to the case with replicate measurements by using LME models. This approach will be discussed in due course.

1.7   Coefficient of Repeatability

Bland and Altman (1999) strongly recommends the simultaneous estimation of repeatability and agreement by collecting replicated data. Roy (2009) notes the lack of convenience in such calculations. The coefficient of repeatability is a measure of how

well a measurement method agrees with itself over replicate measurements (Bland and Altman, 1999).

As mentioned previously, Barnhart et al. (2007) emphasize the importance of repeatability as part of an overall method comparison study. The coefficient of repeatability was proposed by Bland and Altman (1999), and is referenced in subsequent papers, such as Carstensen et al. (2008). BSI (1975) define a coefficient of repeatability as *the value below which the difference between two single test results....may be expected to lie within a specified probability.* Bland and Altman (1999) defines the repeatability coefficient as the upper limits of a prediction interval for the absolute difference between two measurements by the same method on the same item under identical circumstances.

Once the within-item variability for both methods has been estimated, the relevant calculations for the coefficients of repeatability are straightforward. The coefficient is calculated from the within-item variability σ_m^2 as $1.96 \times \sqrt{2} \times \sigma_m = 2.83\sigma_m$. For 95% of subjects, two replicated measurement by the same method will be within this repeatability coefficient.

The coefficient of repeatability may provide the basis for the formulation a formal definition of a 'gold standard'. For example, by determining the ratio of the repeatability coefficient (CR) to the sample mean $\bar{X}$. Advisably the sample size should specified in advance. A gold standard may be defined as the method with the lowest value of $\lambda = CR/\bar{X}$ with $\lambda < 0.1\%$. Similarly, a silver standard may be defined as the method with the lowest value of λ with $0.1\% \leq \lambda < 1\%$. Such thresholds are solely for expository purposes.

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