0.1 Introduction to Limits of Agreement

What is this from?

- Comparing two methods of measurement is normally done by computing limits of agreement (LoA), i.e. prediction limits for a future difference between measurements with the two methods. When the difference is not constant it is not clear what this means, since the difference between the methods depends on the average; hence, unlike the case where the difference is constant, LoA cannot directly be translated into a prediction interval for a measurement by one method given that of another.

- The main point in the paper by Bland and Altman [1] is however different from the outlook in this paper; Bland and Altman mainly discuss whether two methods of measurement can be used interchangeably and how to assess this with the help of proper statistical methods to derive LoA, i.e. prediction limits for differences between two methods. This paper takes as starting point that the classical LoA can be converted to a prediction interval for one method given a measurement by the other (details in the next section). This sort of relationship can be shown in a plot as a line with slope 1 and prediction limits as lines also with slope 1; applicable for the prediction both from method 1 to method 2 and vice versa. In the case of non-constant difference it would be desirable to be able to produce a similar plot, usable both ways. Thus, the aim of this paper is to produce a conversion from one method to another that also applies in the case where the difference between methods is not constant.

- In this paper, I set up a proper model for data for method comparison studies which in the case of constant difference between methods leads to the classical

LoA, and in the case of linear bias gives a simple formula for the prediction. The paper only addresses the situation where only one measurement by each method is available, although replicate measurements by each method are desirable whenever possible [2]. Moreover, the situation with non-constant variance over the range of measurements is not covered either.

0.1.1 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.

How this relates the overall population is unclear. It seems that it depends on an expert to decide whether or not the range of differences is acceptable. In a study A Bland-Altman plots compare two assay methods. It plots the difference between the two measurements on the Y axis, and the average of the two measurements on the X axis

A third element of the Bland-Altman approach, an interval known as 'limits of agreement' is introduced in Bland and Altman (1986) (sometimes referred to in literature as 95% limits of agreement). Limits of agreement are used to assess whether the two methods of measurement can be used interchangeably. Bland and Altman (1986) refer to this as the 'equivalence' of two measurement methods. The specific question to which limits of agreement are intended as the answer to must be established clearly. Bland and Altman (1995) comment that the limits of agreement show '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:

$$LoA = \bar{d} \pm 1.96 S(d) \quad (1)$$

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. (However, in some literature, 2 standard deviations are used instead for simplicity.)

The limits of agreement methodology assumes a constant level of bias throughout the range of measurements. 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 **?** highlight inadequacies in the correct application of limits of agreement, resulting in contradictory estimates of limits of agreement in various papers.

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 1.9 shows the resultant Bland-Altman plot, with the limits of agreement shown in dashed lines.

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. Bland and Altman advises on how to calculate of confidence intervals for the inter-method bias and the limits of agreement. Importantly the authors recommend prior determination of what would and would constitute acceptable agreement, and that sample sizes should be predetermined to give an accurate conclusion.

> 'How far apart measurements can be without causing difficulties will be a question of judgment. Ideally, it should be defined in advance to help in the interpretation of the method comparison and to choose the sample size.'(Bland and Altman, 1986)

0.1.2 Problems with Limits of Agreement

Several problems have been highlighted regarding Limits of Agreement. One is the somewhat arbitrary manner in which they are constructed. While in essence a confidence interval, they are not constructed a such. They are designed for future values. The formulation is also heavily influenced by outliers. An Example in Altman and Bland (1983) demonstrates the effect of recalculating without a particular outlier. Refering to the VCF data set in the same paper, there is more than one outlier.

0.1.3 Limits of Agreement

Bland and Altman (1986) introduces an elaboration of the plot, adding to the plot 'limits of agreement' to the plot. These limits are based upon the standard deviation of the differences. The discussion shall be reverted to these limits of agreement in due course.

0.1.4 Limits Of Agreement

The bias is computed as the average of the difference of paired assays.

If one method is sometimes higher, and sometimes the other method is higher, 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.

0.1.5 Appropriate Use of Limits of Agreement

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 import 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.

Carstensen attends to the issue of repeated data, using the expression replicate to express a repeated measurement on a subject by the same methods. Carstensen formulates the data as follows Repeated measurement - Arrangement of data into groups, based on the series of results of each subject.

0.2 Regression-based Limits of Agreement

Assuming that there will be no curvature in the scatter-plot, the methodology regresses the difference of methods (d) on the average of those methods (a) with a simple intercept slope model; $\hat{d} = b_0 + b_1 a$. Should the slope b_1 be found to be negligible, $\hat{d}$ takes the value $\bar{d}$.

The next step to take in calculating the limits is also a regression, this time of the residuals as a function of the scale of the measurements, expressed by the averages a_i; $\hat{R} = c_0 + c_1 a_i$

With reference to absolute values following a half-normal distribution with mean

$\sigma\sqrt{\frac{2}{\pi}}$, Bland and Altman (1999) formulate the regression based limits of agreement as follows

$$\hat{d} \pm 1.96\sqrt{\frac{\pi}{2}}\hat{R} = \hat{d} \pm 2.46\hat{R} \tag{2}$$

0.3 Limits of agreement for Carstensen's data

Carstensen et al. (2008) describes the calculation of the limits of agreement (with the inter-method bias implicit) for both data sets, based on his formulation;

$$\hat{\alpha}_1 - \hat{\alpha}_2 \pm 2\sqrt{2\hat{\tau}^2 + \hat{\sigma}_1^2 + \hat{\sigma}_2^2}.$$

For the 'Fat' data set, the inter-method bias is shown to be 0.045. The limits of agreement are $(-0.23, 0.32)$

Carstensen demonstrates the use of the interaction term when computing the limits of agreement for the 'Oximetry' data set. When the interaction term is omitted, the limits of agreement are $(-9.97, 14.81)$. Carstensen advises the inclusion of the interaction term for linked replicates, and hence the limits of agreement are recomputed as $(-12.18, 17.12)$.

0.4 Limits of Agreement

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. A different sample would give different limits of agreement. Bland and Altman (1986) advance a formulation for confidence intervals of the inter-method bias and the limits of agreement. These calculations employ quantiles of the 't' distribution with $n-1$ degrees of freedom.

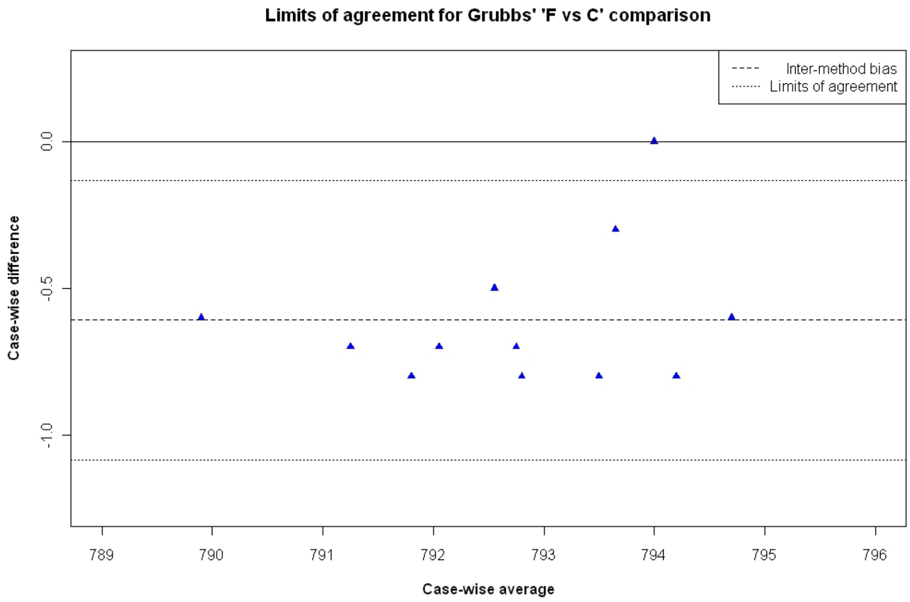

Figure 1: Bland-Altman plot with limits of agreement

0.4.1 Inferences on Bland-Altman estimates

Bland and Altman (1999) advises on how to calculate confidence intervals for the inter-method bias and limits of agreement. For the inter-method bias, the confidence interval is a 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

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

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.

A 95% confidence interval can be determined, by means of the t distribution with

$n - 1$ degrees of freedom. However, Bland and Altman (1999) comment that such calculations may be 'somewhat optimistic' on account of the associated assumptions not being realized.

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