0.1 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 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 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. (Some accounts of Bland-Altman plots use a multiple of 2 standard deviations 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 and would constitute acceptable agreement, and that sample sizes should be predetermined to give an accurate conclusion. However Mantha et al. (2000)

highlights inadequacies in the correct application of limits of agreement, resulting in contradictory estimates limits of agreement in various papers.

> "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)".

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.

0.2 Limits of Agreement

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

with $\bar{d}$ as the estimate of the inter method bias, s_d as the standard deviation of the differences and 1.96 (sometimes rounded to 2) is the 95% quantile for the standard normal distribution. 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 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.

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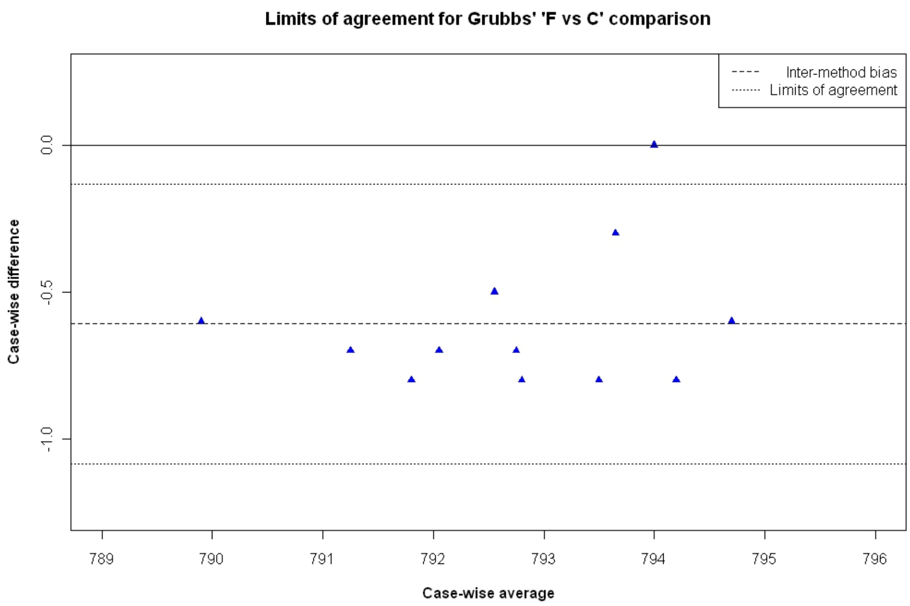

Figure 1: Bland-Altman plot with limits of agreement

0.2.1 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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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: $\bar{d} \pm t_{(0.5\alpha,n-1)} S_d/\sqrt{n}$. 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

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0.2.3 Formal definition 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'.

Limits of agreement have very similar construction to Shewhart control limits. 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 equivalent to Shewhart control limits. Importantly the parameters used to determine the Shewhart limits are not based on any sample used for an analysis, but on the process's historical 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) offers an alternative formulation, a 95% prediction interval for the difference

$$\bar{d} \pm t_{(0.975,n-1)} s_d \sqrt{1 + \frac{1}{n}}$$

where n is the number of subjects. Carstensen is careful to consider the effect of the sample size on the interval width, adding that only for 61 or more subjects is there a quantile less than 2.

Luiz et al. (2003) offers an alternative description of limits of agreement, this time 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. 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'.

The prevalence of contradictory definitions of what limits of agreement strictly are will inevitably attenuate the poor standard of reporting using limits of agreement, as mentioned by Mantha et al. (2000).

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

where n is the number of subjects. Carstensen is careful to consider the effect of the sample size on the interval width, adding that only for 61 or more subjects is the quantile less than 2.

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