

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:

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

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.

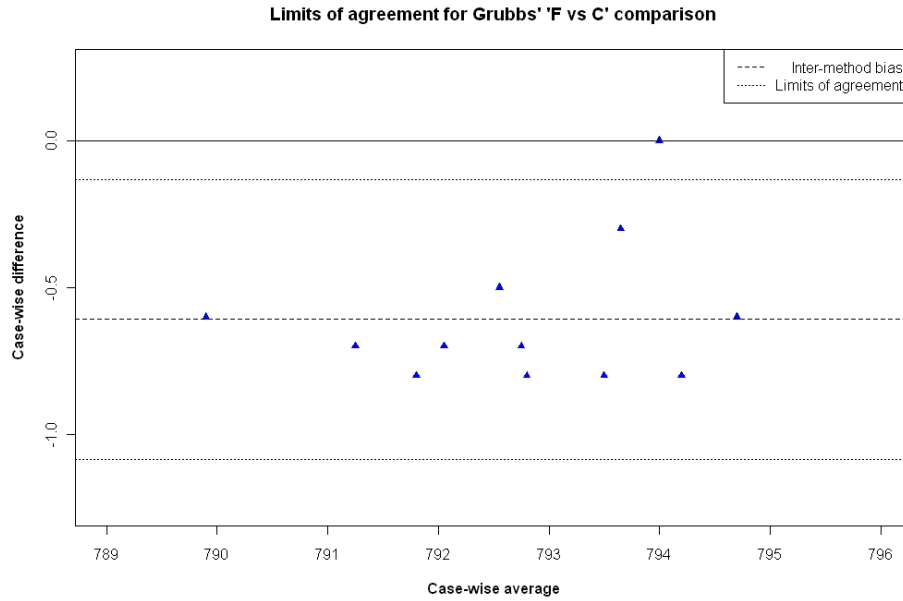


Figure 0.1.1: Bland-Altman plot with limits of agreement

0.1.1 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).

0.1.2 Replicate Measurements

Thus far, the formulation for comparison of two measurement methods is one where one measurement by each method is taken on each subject. Should there be two or more measurements by each methods, these measurement are known as ‘replicate mea-

surements’. Carstensen et al. (2008) recommends the use of replicate measurements, but acknowledges the additional computational complexity.

Bland and Altman (1986) address this problem by offering two different approaches. The premise of the first approach is that replicate measurements can be treated as independent measurements. The second approach is based upon using the mean of the each group of replicates as a representative value of that group. Using either of these approaches will allow an analyst to estimate the inter method bias.

However, because of the removal of the effects of the replicate measurements error, this would cause the estimation of the standard deviation of the differences to be unduly small. Bland and Altman (1986) propose a correction for this.

Carstensen et al. (2008) takes issue with the limits of agreement based on mean values of replicate measurements, in that they can only be interpreted as prediction limits for difference between means of repeated measurements by both methods, as opposed to the difference of all measurements. Incorrect conclusions would be caused by such a misinterpretation. Carstensen et al. (2008) demonstrates how the limits of agreement calculated using the mean of replicates are ‘much too narrow as prediction limits for differences between future single measurements’. This paper also comments that, while treating the replicate measurements as independent will cause a downward bias on the limits of agreement calculation, this method is preferable to the ‘mean of replicates’ approach.

0.1.3 Bland-Altman correlation test

The approach proposed by Altman and Bland (1983) is a formal test on the Pearson correlation coefficient of case-wise differences and means (ρ_{AD}). According to the authors, this test is equivalent to the ‘Pitman Morgan Test’. For the Grubbs data, the correlation coefficient estimate (r_{AD}) is 0.2625, with a 95% confidence interval of (-0.366, 0.726) estimated by Fishers ‘ r to z ’ transformation (Cohen, Cohen, West, and Aiken, Cohen et al.). The null hypothesis ($\rho_{AD} = 0$) fail to be rejected. Consequently

the null hypothesis of equal variances of each method would also fail to be rejected. There has been no further mention of this particular test in Bland and Altman (1986), although Bland and Altman (1999) refers to Spearman's rank correlation coefficient. Bland and Altman (1999) comments 'we do not see a place for methods of analysis based on hypothesis testing'. Bland and Altman (1999) also states that consider structural equation models to be inappropriate.

0.1.4 Identifiability

Dunn (2002) highlights an important issue regarding using models such as these, the identifiability problem. This comes as a result of there being too many parameters to be estimated. Therefore assumptions about some parameters, or estimators used, must be made so that others can be estimated. For example in literature the variance ratio $\lambda = \frac{\sigma_1^2}{\sigma_2^2}$ must often be assumed to be equal to 1 (Linnet, 1998). Dunn (2002) considers methodologies based on two methods with single measurements on each subject as inadequate for a serious study on the measurement characteristics of the methods. This is because there would not be enough data to allow for a meaningful analysis. There is, however, a contrary argument that in many practical settings it is very difficult to get replicate observations when the measurement method requires invasive medical procedure.

Bradley and Blackwood (1989) offers a formal simultaneous hypothesis test for the mean and variance of two paired data sets. Using simple linear regression of the differences of each pair against the sums, a line is fitted to the model, with estimates for intercept and slope ($\hat{\beta}_0$ and $\hat{\beta}_1$). The null hypothesis of this test is that the mean (μ) and variance (σ^2) of both data sets are equal if the slope and intercept estimates are equal to zero (i.e $\sigma_1^2 = \sigma_2^2$ and $\mu_1 = \mu_2$ if and only if $\beta_0 = \beta_1 = 0$)

A test statistic is then calculated from the regression analysis of variance values (Bradley and Blackwood, 1989) and is distributed as ' F ' random variable. The degrees of freedom are $\nu_1 = 2$ and $\nu_2 = n - 2$ (where n is the number of pairs). The critical

value is chosen for $\alpha\%$ significance with those same degrees of freedom. Bartko (1994) amends this methodology for use in method comparison studies, using the averages of the pairs, as opposed to the sums, and their differences. This approach can facilitate simultaneous usage of test with the Bland-Altman methodology. Bartko's test statistic take the form:

$$F.test = \frac{(\Sigma d^2) - SSReg}{2MSReg}$$

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Averages	1	0.04	0.04	0.74	0.4097
Residuals	10	0.60	0.06		

Table 0.1.1: Regression ANOVA of case-wise differences and averages for Grubbs Data

For the Grubbs data, $\Sigma d^2 = 5.09$, $SSReg = 0.60$ and $MSreg = 0.06$ Therefore the test statistic is 37.42, with a critical value of 4.10. Hence the means and variance of the Fotobalk and Counter chronometers are assumed to be simultaneously equal.

Importantly, this methodology determines whether there is both inter-method bias and precision present, or alternatively if there is neither present. It has previously been demonstrated that there is a inter-method bias present, but as this procedure does not allow for separate testing, no conclusion can be drawn on the comparative precision of both methods.

0.2 Regression Methods

Conventional regression models are estimated using the ordinary least squares (OLS) technique, and are referred to as 'Model I regression' (Cornbleet and Cochrane, 1979; Ludbrook, 1997). A key feature of Model I models is that the independent variable is assumed to be measured without error. As often pointed out in several papers (Altman and Bland, 1983; Ludbrook, 1997), this assumption invalidates simple linear

regression for use in method comparison studies, as both methods must be assumed to be measured with error.

The use of regression models that assumes the presence of error in both variables X and Y have been proposed for use instead (Cornbleet and Cochrane, 1979; Ludbrook, 1997). These methodologies are collectively known as ‘Model II regression’. They differ in the method used to estimate the parameters of the regression.

Regression estimates depend on formulation of the model. A formulation with one method considered as the X variable will yield different estimates for a formulation where it is the Y variable. With Model I regression, the models fitted in both cases will entirely different and inconsistent. However with Model II regression, they will be consistent and complementary.

Regression approaches are useful for a making a detailed examination of the biases across the range of measurements, allowing bias to be decomposed into fixed bias and proportional bias. Fixed bias describes the case where one method gives values that are consistently different to the other across the whole range. Proportional bias describes the difference in measurements getting progressively greater, or smaller, across the range of measurements. A measurement method may have either an attendant fixed bias or proportional bias, or both. (?). Determination of these biases shall be discussed in due course.

0.3 Limits of Agreement

Computing limits of agreement features prominently in many method comparison studies, further to Bland and Altman (1986, 1999). 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 (i.e. independent data), 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. ? computes the limits of agreement to the case with replicate measurements by using LME models.

0.4 Outline of Thesis

Thus the study of method comparison is introduced. The intention of this thesis is to progress the study of method comparison studies, using a statistical method known as Linear mixed effects models. Chapter two shall describe linear mixed effects models, and how the use of the linear mixed effects models have so far extended to method comparison studies. Implementations of important existing work shall be presented, using the R programming language.

Model diagnostics are an integral component of a complete statistical analysis. In chapter three model diagnostics shall be described in depth, with particular emphasis on linear mixed effects models, further to chapter two.

For the fourth chapter, important linear mixed effects model diagnostic methods shall be extended to method comparison studies, and proposed methods shall be demonstrated on data sets that have become well known in literature on method comparison. The purpose is to both calibrate these methods and to demonstrate applications for them. The last chapter shall focus on robust measures of important parameters such as agreement.

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