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Chapter 1

Formal Models and Tests

1.1 Formal Testing

The Bland-Altman plot is a simple tool for inspection of the data, but in itself offers little in the way of formal testing. It is upon the practitioner opinion to judge the outcome of the methodology. To this end, the approach proposed by Altman and Bland (1983) is a formal test on the Pearson correlation coefficient of casewise differences and means (ρ_{AD}). According to the authors, this test is equivalent to a well established tests for equality of variances, known as the 'Pitman Morgan Test' (Pitman, 1939; Morgan, 1939).

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 (ρ_{AD} =0) would fail to be rejected. Consequently the null hypothesis of equal variances of each method would also fail to be rejected.

There has no been no further mention of this particular test in the subsequent article published by Bland and Altman, although Bland and Altman (1999) refers to Spearmans' rank correlation coefficient.

The case-wise differences and means are calculated as $d_i = x_i - y_i$ and $a_i = (x_i + y_i)/2$

respectively. Both d_i and a_i are assumed to follow a bivariate normal distribution with $E(d_i) = \mu_d = \mu_1 - \mu_2$ and $E(a_i) = \mu_a = (\mu_1 + \mu_2)/2$. The variance matrix $\Sigma_{(a,d)}$ is

$$\Sigma_{(a,d)} = \begin{bmatrix} \sigma_1^2 + \sigma_2^2 & \frac{1}{2}(\sigma_1^2 - \sigma_2^2) \\ \frac{1}{2}(\sigma_1^2 - \sigma_2^2) & \sigma^2 + \frac{1}{4}(\sigma_1^2 + \sigma_2^2) \end{bmatrix}. \tag{1.1}$$

1.2 Classical model for single measurements

Before continuing, we require a simple model to describe a measurement by method m. Carstensen (2004) presents a model to describe the relationship between a value of measurement and its real value. The non-replicate case is considered first, as it is the context of the Bland Altman plots. This model assumes that inter-method bias is the only difference between the two methods.

This model is based on measurements y_{mi} by method $m = 1, 2$ on item $i = 1, 2 \ldots$. We use the term *item* to denote an individual, subject or sample, to be measured, being randomly sampled from a population

$$y_{mi} = \alpha_m + \mu_i + e_{mi}, \qquad e_{mi} \sim \mathcal{N}(0, \sigma_m^2). \tag{1.2}$$

Here α_m is the fixed effect associated with method m, μ_i is the true value for subject i (fixed effect) and e_{mi} is a random effect term for errors.

The case-wise differences are expressed as $d_i = y_{1i} - y_{2i}$. Even though the separate variances can not be identified, their sum can be estimated by the empirical variance of the differences, using standard statistical theory. The covariance matrix for case-wise differences can be specified as

$$\Sigma = \begin{pmatrix} \sigma_1^2 + \sigma_2^2 & \frac{1}{2}(\sigma_1^2 - \sigma_2^2) \\ \frac{1}{2}(\sigma_1^2 - \sigma_2^2) & \sigma_b^2 + \frac{1}{4}(\sigma_1^2 + \sigma_2^2) \end{pmatrix}.$$

Likewise the separate α can not be estimated, only their difference can be estimated as $\bar{d}$ (i.e. the inter-method bias). This model implies that the difference between the paired measurements can be expressed as

$$d_i = y_{1i} - y_{2i} \sim \mathcal{N}(\alpha_1 - \alpha_2, \sigma_1^2 + \sigma_2^2).$$

Importantly, this is independent of the item levels μ_i. As the case-wise differences are of interest, the parameters of interest are the fixed effects for methods α_m.

1.3 Move to Chapter 3

Carstensen (2004) also advocates the use of linear mixed models in the study of method comparisons. The model is constructed to describe the relationship between a value of measurement and its real value. The non-replicate case is considered first, as it is the context of the Bland-Altman plots. This model assumes that inter-method bias is the only difference between the two methods. A measurement y_{mi} by method m on individual i is formulated as follows;

$$y_{mi} = \alpha_m + \mu_i + e_{mi} \qquad (e_{mi} \sim N(0, \sigma^2_m)) \tag{1.3}$$

The differences are expressed as $d_i = y_{1i} - y_{2i}$ For the replicate case, an interaction term c is added to the model, with an associated variance component. All the random effects are assumed independent, and that all replicate measurements are assumed to be exchangeable within each method.

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir} \qquad (e_{mi} \sim N(0, \sigma^2_m), c_{mi} \sim N(0, \tau^2_m)) \tag{1.4}$$

1.4 Model for single measurement observations

Kinsella (1986) formulates a model for single measurement observations for a method comparison study as a linear mixed effects model, i.e. model that additively combine fixed effects and random effects.

$$Y_{ij} = \quad \mu + \beta_j + u_i + \epsilon_{ij} \qquad i = 1, \ldots, n \qquad j = 1, 2$$

The true value of the measurement is represented by μ while the fixed effect due to method j is β_j. For simplicity these terms can be combined into single terms;

$\mu_1 = \mu + \beta_1$ and $\mu_2 = \mu + \beta_2$. The inter-method bias is the difference of the two fixed effect terms, $\beta_1 - \beta_2$. Each individual is assumed to give rise to a random error, represented by u_i. This random effects term is assumed to have mean zero and be normally distributed with variance σ^2. There is assumed to be an attendant error for each measurement on each individual, denoted ϵ_{ij}. This is also assumed to have mean zero. The variance of measurement error for both methods are not assumed to be identical for both methods variance, hence it is denoted σ^2_j. The set of observations (x_i, y_i) by methods X and Y are assumed to follow a bivariate normal distribution with expected values $E(x_i) = \mu_i$ and $E(y_i) = \tau_i$ respectively. The variance covariance of the observations $\boldsymbol{\Sigma}$ is given by

$$\boldsymbol{\Sigma} = \begin{bmatrix} \sigma^2 + \sigma^2_1 & \sigma^2 \\ \sigma^2 & \sigma^2 + \sigma^2_2 \end{bmatrix}$$

1.5 Thompson 1963: Model Formulation and Formal Testing

Kinsella (1986) formulates a model for un-replicated observations for a method comparison study as a mixed model.

$$\begin{aligned} Y_{ij} = &\quad \mu_j + S_i + \epsilon_{ij} \quad i = 1, 2...n \quad j = 1, 2 \\ & S \sim N(0, \sigma^2_s) \qquad \epsilon_{ij} \sim N(0, \sigma^2_j) \end{aligned} \tag{1.5}$$

As with all mixed models, the variance of each observation is the sum of all the associated variance components.

$$\begin{aligned} var(Y_{ij}) = &\quad \sigma^2_s + \sigma^2_j \\ cov(Y_{i1}, Y_{i2}) = &\quad \sigma^2_s \end{aligned} \tag{1.6}$$

As with all mixed models, the variance of each observation is the sum of all the associated variance components.

$$
\begin{aligned}
var(Y_{ij}) = &\quad \sigma^2_s + \sigma^2_j \\
cov(Y_{i1}, Y_{i2}) = &\quad \sigma^2_s
\end{aligned}
\tag{1.7}
$$

Grubbs (1948) offers maximum likelihood estimators, commonly known as Grubbs estimators, for the various variance components:

$$
\begin{aligned}
\hat{\sigma^2_s} &= \sum \frac{(x_i - \bar{x})(y_i - \bar{y})}{n-1} &= Sxy \\
\hat{\sigma^2_1} &= \sum \frac{(x_i - \bar{x})^2}{n-1} &= S^2x - Sxy \\
\hat{\sigma^2_2} &= \sum \frac{(y_i - \bar{y})^2}{n-1} &= S^2y - Sxy
\end{aligned}
\tag{1.8}
$$

The standard error of these variance estimates are:

$$
\begin{aligned}
var(\sigma^2_1) = &\quad \frac{2\sigma^4_1}{n-1} + \quad \frac{\sigma^2_S\sigma^2_1 + \sigma^2_S\sigma^2_2 + \sigma^2_1\sigma^2_2}{n-1} \\
var(\sigma^2_2) = &\quad \frac{2\sigma^4_2}{n-1} + \quad \frac{\sigma^2_S\sigma^2_1 + \sigma^2_S\sigma^2_2 + \sigma^2_1\sigma^2_2}{n-1}
\end{aligned}
\tag{1.9}
$$

Kinsella (1986) demonstrates the estimation of the variance terms and relative precisions relevant to a method comparison study, with attendant confidence intervals for both. The measurement model introduced by Grubbs (1948, 1973) provides a formal procedure for estimating the variances σ^2, σ^2_1 and σ^2_2. Grubbs (1948) offers estimates, commonly known as Grubbs estimators, for the various variance components. These estimates are maximum likelihood estimates, which shall be revisited in due course.

$$
\begin{aligned}
\hat{\sigma^2} &= \sum \frac{(x_i - \bar{x})(y_i - \bar{y})}{n-1} = Sxy \\
\hat{\sigma^2_1} &= \sum \frac{(x_i - \bar{x})^2}{n-1} = S^2x - Sxy \\
\hat{\sigma^2_2} &= \sum \frac{(y_i - \bar{y})^2}{n-1} = S^2y - Sxy
\end{aligned}
$$

The inter-method bias is the difference of the two fixed effect terms, $\beta_1 - \beta_2$.

Kinsella (1986) demonstrates how the Grubbs estimators for the error variances can be calculated using the difference values, providing a worked example on a data set.

$$\begin{aligned}\hat{\sigma_1^2} &= \sum (y_{i1} - \bar{y1})(D_i - \bar{D}) \qquad (1.10)\\ \hat{\sigma_2^2} &= \sum (y_{i2} - \bar{y_2})(D_i - \bar{D})\end{aligned}$$

Thompson (1963) presents confidence intervals for the relative precisions of the measurement methods, $\Delta_j = \sigma^2_S/\sigma^2_j$ (where $j = 1, 2$), as well as the variances σ^2_S, σ^2_1 and σ^2_2.

$$\Delta_1 > \quad \frac{C_{xy} - t(|A|/n-2))^{\frac{1}{2}}}{C_x - C_{xy} + t(|A|/n-2))^{\frac{1}{2}}} \qquad (1.11)$$

where

$$\begin{aligned}C_x &= \quad (n-1)S^2_x\\ C_{xy} &= \quad (n-1)S_{xy}\\ C_y &= \quad (n-1)S^2_y\\ A &= \quad C_x \times C_y - (C_{xy})^2\end{aligned}$$

t is the $100(1 - \alpha/2)\%$ quantile of Student's t distribution with $n - 2$ degrees of freedom. Δ_2 can be found by changing C_y for C_x. A lower confidence limit can be found by calculating the square root. This inequality may also be used for hypothesis testing.

For the interval estimates for the variance components, Thompson (1963) presents three relations that hold simultaneously with probability $1 - 2\alpha$ where $2\alpha = 0.01$ or 0.05.

$$\begin{aligned}|\sigma^2 - C_{xy}K| &\leqslant M(C_xC_y)^{\frac{1}{2}} \qquad (1.12)\\ |\sigma^2_1 - (C_x - C_{xy})K| &\leqslant M(C_x(C_x + C_y - 2C_{xy}))^{\frac{1}{2}}\\ |\sigma^2_2 - (C_y - C_{xy})K| &\leqslant M(C_y(C_x + C_y - 2C_{xy}))^{\frac{1}{2}}\end{aligned}$$

1.6 Formal Models and Tests

Thompson (1963) defines $\Delta_j = \sigma^2/\sigma_j^2, j = 1, 2$, to be a measure of the relative precision of the measurement methods, and demonstrates how to make statistical inferences about Δ_j. Based on the following identities,

$$\begin{aligned} C_x &= (n-1)S_x^2, \\ C_{xy} &= (n-1)S_{xy}, \\ C_y &= (n-1)S_y^2, \\ |A| &= C_x \times C_y - (C_{xy})^2, \end{aligned}$$

the confidence interval limits of Δ_1 are

$$\frac{C_{xy} - t(\frac{|A|}{n-2}))^{\frac{1}{2}}}{C_x - C_{xy} + t(\frac{|A|}{n-2}))^{\frac{1}{2}}} < \Delta_1 < \frac{C_{xy} + t(\frac{|A|}{n-2}))^{\frac{1}{2}}}{C_x - C_{xy} - t(\frac{|A|}{n-1}))^{\frac{1}{2}}}$$

The value t is the $100(1-\alpha/2)\%$ upper quantile of Student's t distribution with $n-2$ degrees of freedom (Kinsella, 1986). The confidence limits for Δ_2 are found by substituting C_y for C_x in (1.2). Negative lower limits are replaced by the value 0. The ratio Δ_2 can be found by interchanging C_y and C_x. A lower confidence limit can be found by calculating the square root. The inequality in equation 1.10 may also be used for hypothesis testing.

Thompson (1963) presents three relations that hold simultaneously with probability $1-2\alpha$ where $2\alpha = 0.01$ or 0.05. Thompson (1963) contains tables for K and M.

$$\begin{aligned} |\sigma^2 - C_{xy}K| &\leqslant M(C_xC_y)^{\frac{1}{2}} \qquad (1.13) \\ |\sigma_1^2 - (C_x - C_{xy})K| &\leqslant M(C_x(C_x + C_y - 2C_{xy}))^{\frac{1}{2}} \\ |\sigma_2^2 - (C_y - C_{xy})K| &\leqslant M(C_y(C_x + C_y - 2C_{xy}))^{\frac{1}{2}} \end{aligned}$$

1.7 Morgan Pitman

An early contribution to formal testing in method comparison was made by both **?** and **?**, in separate contributions. This test assess the equality of population variances. Pitman's test tests for zero correlation between the sums and products.

An early contribution to formal testing in method comparison was made by both Morgan (1939) and Pitman (1939), in separate contributions. The basis of this approach is that the distribution of the original measurements is bivariate normal. Correlation between differences and means is a test statistics for the null hypothesis of equal variances given bivariate normality.

The test of the hypothesis that the variances σ_1^2 and σ_2^2 are equal, which was devised concurrently by Pitman (1939) and Morgan (1939), is based on the correlation of the casewise-differences and sums, d with s, the coefficient being $\rho_{(d,s)} = (\sigma_1^2 - \sigma_2^2)/(\sigma_D \sigma_S)$, which is zero if, and only if, $\sigma_1^2 = \sigma_2^2$. The classical Pitman-Morgan test can be adapted for the correlation value $\rho_{(a,d)}$,and is evaluated as follows;

$$\rho(a,d) = \frac{\sigma_1^2 - \sigma_2^2}{\sqrt{(\sigma_1^2 + \sigma_2^2)(4\sigma_S^2 + \sigma_1^2 + \sigma_2^2)}} \tag{1.14}$$

The basis of this approach is that the distribution of the original measurements is bivariate normal. Morgan and Pitman noted that the correlation coefficient depends upon the difference $\sigma_1^2 - \sigma_2^2$, being zero if and only if $\sigma_1^2 = \sigma_2^2$.

The classical Pitman-Morgan test is a hypothesis test for equality of the variance of two data sets; $\sigma_1^2 = \sigma_2^2$, based on the correlation value $\rho_{a,d}$,and is evaluated as follows;

$$\rho(a,d) = \frac{\sigma_1^2 - \sigma_2^2}{\sqrt{(\sigma_1^2 + \sigma_2^2)(4\sigma_S^2 + \sigma_1^2 + \sigma_2^2)}} \tag{1.15}$$

The correlation constant takes the value zero if, and only if, the two variances are equal.

Morgan and Pitman noted that the correlation coefficient depends upon the difference $\sigma_1^2 - \sigma_2^2$, being zero if and only if $\sigma_1^2 = \sigma_2^2$. Therefore a test of the hypothesis

$H : \sigma_1^2 = \sigma_2^2$ is equivalent to a test of the hypothesis $H : \rho(D, A) = 0$. This corresponds to the well-known t test for a correlation coefficient with $n - 2$ degrees of freedom.

Bartko (1994) describes the Morgan-Pitman test as identical to the test of the slope equal to zero in the regression of Y_{i1} on Y_{12}, a result that can be derived using straightforward algebra.

1.8 Morgan Pitman

The test of the hypothesis that the variance of both methods are equal is based on the correlation value $\rho_{D,A}$ which is evaluated as follows;

$$\rho(D, A) = \frac{\sigma_1^2 - \sigma_2^2}{\sqrt{(\sigma_1^2 + \sigma_2^2)(4\sigma_S^2 + \sigma_1^2 + \sigma_2^2)}} \tag{1.16}$$

The correlation constant takes the value zero if, and only if, the two variances are equal. Therefore a test of the hypothesis $H : \sigma_1^2 = \sigma_2^2$ is equivalent to a test of the hypothesis $H : \rho(D, A) = 0$. The corresponds to the well-known t test for a correlation coefficient with $n - 2$ degrees of freedom.

Bartko (1994) describes the Morgan-Pitman test as identical to the test of the slope equal to zero in the regression of Y_{i1} on Y_{12}, adding that this result can be shown using straightforward algebra.

The Pitman-Morgan test for equal variances is based on the correlation of D with S. The correlation coefficient is zero if, and only if, the variances are equal. The test statistic is the familiar t-test with n-2 degree of freedom. Bradley and Blackwood (1989) construct the conditional expectation of D given S as linear model. They used this result to propose a test of the joint hypothesis of the mean difference and equal variances. If the intercept and slope estimates are zero, the two methods have the same mean and variance. The Pitman-Morgan test is equivalent to the marginal test of the slope estimate in Bradley-Blackwoods model.

1.9 Identifiability

Dunn (2002) highlights an important issue regarding using models such as structural equation modelling, which is 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 the literature, the variance ratio $\lambda = \frac{\sigma^2_1}{\sigma^2_2}$ must often be assumed to be equal to 1 (Linnet, 1998). Dunn (2002) considers approaches 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 counter-argument that in many practical settings it is very difficult to get replicate observations when, for example, the measurement method requires invasive medical procedure.

1.10 Measurement Error Models

Dunn (2002) proposes a measurement error model for use in method comparison studies. Consider n pairs of measurements X_i and Y_i for $i = 1, 2, ...n$.

$$X_i = \tau_i + \delta_i \tag{1.17}$$

$$Y_i = \alpha + \beta\tau_i + \epsilon_i$$

In the above formulation is in the form of a linear structural relationship, with τ_i and $\beta\tau_i$ as the true values , and δ_i and ϵ_i as the corresponding measurement errors. In the case where the units of measurement are the same, then $\beta = 1$.

$$E(X_i) = \tau_i \tag{1.18}$$

$$E(Y_i) = \alpha + \beta\tau_i$$

$$E(\delta_i) = E(\epsilon_i) = 0$$

The value α is the inter-method bias between the two methods.

$$z_0 = d = 0 \tag{1.19}$$

$$z_{n+1} = z_n^2 + c \tag{1.20}$$

1.11 Carstensen Model for Replicate Measurements

Carstensen et al. (2008) develop their model from a standard two-way analysis of variance model, reformulated for the case of replicate measurements, with random effects terms specified as appropriate. For the replicate case, an interaction term c is added to the model, with an associated variance component. Their model describing y_{mir}, again the rth replicate measurement on the ith item by the mth method ($m = 1, 2$, $i = 1, \ldots, N$, and $r = 1, \ldots, n$), can be written as

$$y_{mir} = \alpha_m + \mu_i + a_{ir} + c_{mi} + \epsilon_{mir}. \tag{1.21}$$

Again, the fixed effects α_m and μ_i represent the intercept for method m and the 'true value' for item i respectively. The random-effect terms comprise an item-by-replicate interaction term $a_{ir} \sim \mathcal{N}(0, \varsigma^2)$, a method-by-item interaction term $c_{mi} \sim \mathcal{N}(0, \tau_m^2)$, and model error terms $\varepsilon \sim \mathcal{N}(0, \varphi_m^2)$. All random-effect terms are assumed to be independent. For the case when replicate measurements are assumed to be exchangeable for item i, a_{ir} can be removed.

The model expressed in (2) describes measurements by m methods, where $m = \{1, 2, 3 \ldots\}$. Based on the model expressed in (2), Carstensen et al. (2008) compute the limits of agreement as

$$\alpha_1 - \alpha_2 \pm 2\sqrt{\tau_1^2 + \tau_2^2 + \varphi_1^2 + \varphi_2^2}$$

Carstensen et al. (2008) notes that, for $m = 2$, separate estimates of τ_m^2 can not be obtained. To overcome this, the assumption of equality, i.e. $\tau_1^2 = \tau_2^2$ is required.

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir}, \qquad e_{mi} \sim \mathcal{N}(0, \sigma_m^2), \quad c_{mi} \sim \mathcal{N}(0, \tau_m^2). \tag{1.22}$$

1.12 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 (ρ_{AD} =0) fail to be rejected. Consequently the null hypothesis of equal variances of each method would also fail to be rejected. There has no 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.

1.13 Paired sample *t* test

Bartko (1994) discusses the use of the well known paired sample t test to test for inter-method bias; $H : \mu_d = 0$. The test statistic is distributed a t random variable with $n-1$ degrees of freedom and is calculated as follows,

$$t^{*} = \frac{\bar{d}}{\frac{s_d}{\sqrt{n}}} \tag{1.23}$$

where $\bar{d}$ and s_d is the average of the differences of the n observations. Only if the two methods show comparable precision then the paired sample student t-test is appropriate for assessing the magnitude of the bias.

Chapter 2

Regression Procedures

2.1 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.

2.2 Regression Methods

Scatterplots are recommended by Altman and Bland (1983) for an initial examination of the data, facilitating an initial judgement and helping to identify potential outliers. They are not useful for a thorough examination of the data. O'Brien et al. (1990) notes that data points will tend to cluster around the line of equality, obscuring interpretation.

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.

Ludbrook (1997, 2002) criticizes Bland-Altman plots on the basis that they presents 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 effect they would have on the limits of agreeement, but offer no guidance on how to correct for those effects.

2.2.1 Decomposition of Inter-Method Bias

Regression approaches are useful for a making a detailed examination of the biases across the range of measurements, allowing inter-method 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.

Constant or proportional bias in method comparison studies using linear regression can be detected by an individual test on the intercept or the slope of the line regressed from the results of the two methods to be compared.

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 (Ludbrook, 2002).

If the basic assumptions underlying linear regression are not met, the regression equation, and consequently the estimations of bias are undermined. Outliers are a source of error in regression estimates.

2.2.2 Inference Procedures

A 95% confidence interval for the intercept estimate can be used to test the intercept, and hence fixed bias, is equal to zero. This hypothesis is accepted if the confidence interval for the estimate contains the value 0 in its range. Should this be, it can be concluded that fixed bias is not present. Conversely, if the hypothesis is rejected, then it is concluded that the intercept is non zero, and that fixed bias is present.

Testing for proportional bias is a very similar procedure. The 95% confidence interval for the slope estimate can be used to test the hypothesis that the slope is equal to 1. This hypothesis is accepted if the confidence interval for the estimate contains the value 1 in its range. If the hypothesis is rejected, then it is concluded that the slope is significant different from 1 and that a proportional bias exists.

2.3 Incorrect Techniques: Simple Linear Regression

2.3.1 Regression Analysis

Another inappropriate approach is the regressing one set of measurements against the other. According to this methodology the measurement methods could considered equivalent if the confidence interval for the regression coefficient included 1. Analysts sometimes use least squares (referred to by Ludbrook as Model I) regression analysis to calibrate one method of measurement against another. In this technique, the sum of the squares of the vertical deviations of y values from the line is minimized. This approach is invalid, because both y and x values are attended by random error.

2.3.2 The Identity Plot

This is a simple graphical approach, advocated by Bland and Altman (1986), that yields a cursory examination of how well the measurement methods agree. In the case of good agreement, the co-variates of the plot accord closely with the $X = Y$ line.

2.3.3 Advantages of Regression Approaches for MCS

- These methods can be employed in conversion problems.
- Bland and Altman have stated that regression analysis offers insights into MCS problems.

2.3.4 Disadvantages

- Regression methods are uninformative about the variability of the differences.
- Regression methods can determine the presence of bias, and the levels of constant bias and proportional bias thereof Ludbrook (1997, 2002).

- **Constant Bias** This is a form of systematic deviations estimated as the average difference between the test and the reference method.

- **Proportional Bias** Two methods may agree on average, but they may exhibit differences over a range of measurements.

Two methods may agree on average, but they may exhibit differences over a range of measurements. Proportional Bias is a difference in the two measures which is proportional to the scale of the measurement.

Using a naive estimation of bias, such as the mean of differences, it may incorrectly indicate absence of bias, by yielding a mean difference close to zero. This would be caused by positive differences in the measurements at one end of the range of measurements being canceled out by negative differences at the other end of the scale.

2.4 Blackwood-Bradley Model

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 $\sigma^2_1 = \sigma^2_2$ and $\mu_1 = \mu_2$ if and only if $\beta_0 = \beta_1 = 0$).

Bradley and Blackwood (1989) have developed a regression based procedure for assessing the agreement. This approach performs a simultaneous test for the equivalence of means and variances of the respective methods. The Bradley Blackwood test is a simultaneous test for bias and precision. They propose a regression approach which fits D on M, where D is the difference and average of a pair of results. 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 $\hat{\beta}_1$).

$$D = (X_1 - X_2) \tag{2.1}$$

$$M = (X_1 + X_2)/2 \tag{2.2}$$

The Bradley Blackwood Procedure fits D on M as follows:

$$D = \beta_0 + \beta_1 M \tag{2.3}$$

This technique offers a formal simultaneous hypothesis test for the mean and variance of two paired data sets. 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 $\beta_0 = \beta_1 = 0$)

Both beta values, the intercept and slope, are derived from the respective means and standard deviations of their respective data sets.

We determine if the respective means and variances are equal if both beta values are simultaneously equal to zero. The Test is conducted using an F test, calculated from the results of a regression of D on M.

Russell et al have suggested this method be used in conjunction with a paired t-test , with estimates of slope and intercept.

Bradley and Blackwood have developed a regression based approach assessing the agreement.

We have identified this approach to be examined to see if it can be used as a foundation for a test perform a test on means and variances individually.

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 $\nu_1 = n - 2$ (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 approach for use in method comparison studies, using the averages of the pairs, rather than the sums, and the corresponding case-wise differences. This approach can facilitate simultaneous usage of test with the Bland-Altman approach. Bartko's test statistic take the form:

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

2.4.1 Application to the 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 approach 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.

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

2.5 Bradley-Blackwood Method

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 $\nu_1 = n - 2$ (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:

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

2.6 Bradley-Blackwood Test (Kevin Hayes Talk)

This work considers the problem of testing $\mu_1 = \mu_2$ and $\sigma_1^2 = \sigma_2^2$ using a random sample from a bivariate normal distribution with parameters $(\mu_1, \mu_2, \sigma_1^2, \sigma_2^2, \rho)$.

The new contribution is a decomposition of the Bradley-Blackwood test statistic (*Bradley and Blackwood, 1989*)for the simultaneous test of $\mu_1 = \mu_2$; $\sigma_1^2 = \sigma_2^2$ as a sum of two statistics.

One is equivalent to the Pitman-Morgan (*Pitman, 1939; Morgan, 1939*) test statistic for $\sigma_1^2 = \sigma_2^2$ and the other one is a new alternative to the standard paired-t test of $\mu_D = \mu_1 = \mu_2 = 0$.

Surprisingly, the classic Student paired-t test makes no assumptions about the equality (or otherwise) of the variance parameters.

The power functions for these tests are quite easy to derive, and show that when $\sigma_1^2 = \sigma_2^2$, the paired t-test has a slight advantage over the new alternative in terms of power, but when $\sigma_1^2 \neq \sigma_2^2$, the new test has substantially higher power than the paired-t test.

While Bradley and Blackwood provide a test on the joint hypothesis of equal means and equal variances their regression based approach does not separate these two issues.

The rejection of the joint hypothesis may be due to two groups with unequal means and unequal variances; unequal means and equal variances, or equal means and unequal variances. We propose an approach for resolving this (model selection) problem in a manner controlling the magnitudes of the relevant type I error probabilities.

2.7 Error-In-Variable Models

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 "Error-In-Variables Models" and "Model II regression". They differ in the method used to estimate the parameters of the regression.

Errors-in-variables models or measurement errors models are regression models that account for measurement errors in the independent variables, as well as the dependent variable.

The Bland Altman Plot is uninformative about the comparative influence of proportional bias and fixed bias. Model II approaches can provide independent tests for both types of bias.

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.

Cornbleet and Cochrane (1979) comparing the three methods, citing studies by other authors, concluding that Deming regression is the most useful of these methods. They found the Bartlett method to be flawed in determining slopes.

However the author point out that *clinical laboratory measurements usually in-*

crease in absolute imprecision when larger values are measured. However one of the assumptions that underline Deming and Mandel regression is constancy of the measurement errors throughout the range of values.

2.8 Deming Regression

As stated previously, the fundamental flaw of simple linear regression is that it allows for measurement error in one variable only. This causes a downward biased slope estimate.

Deming regression is a regression fitting approach that assumes error in both variables. Deming regression is recommended by Cornbleet and Cochrane (1979) as the preferred Model II regression for use in method comparison studies. The sum of squared distances from measured sets of values to the regression line is minimized at an angles specified by the ratio λ of the residual variance of both variables. I When λ is one, the angle is 45 degrees. In ordinary linear regression, the distances are minimized in the vertical directions (Linnet, 1999). In cases involving only single measurements by each method, λ may be unknown and is therefore assumes a value of one. While this will produce biased estimates, they are less biased than ordinary linear regression.

The Bland Altman Plot is uninformative about the comparative influence of proportional bias and fixed bias. Model II approaches, such as Deming regression, can provide independent tests for both types of bias.

For a given λ, Kummel (1879) derived the following estimate that would later be used for the Deming regression slope parameter. The intercept estimate α is simply estimated in the same way as in conventional linear regression, by using the identity $\bar{Y} - \hat{\beta}\bar{X}$;

$$\hat{\beta} = \frac{S_{yy} - \lambda S_{xx} + [(S_{yy} - \lambda S_{xx})^2 + 4\lambda S_{xy}^2]^{1/2}}{2S_{xy}} \tag{2.4}$$

with λ as the variance ratio. As stated previously λ is often unknown, and therefore must be assumed to equal one. Carroll and Ruppert (1996) states that Deming regression is acceptable only when the precision ratio (λ,in their paper as η) is correctly specified, but in practice this is often not the case, with the λ being underestimated. Several candidate models, with varying variance ratios may be fitted, and estimates of the slope and intercept are produced. However no model selection information is available to determine the best fitting model.

As with conventional regression methodologies, Deming regression calculates an estimate for both the slope and intercept for the fitted line, and standard errors thereof. Therefore there is sufficient information to carry out hypothesis tests on both estimates, that are informative about presence of fixed and proportional bias.

A 95% confidence interval for the intercept estimate can be used to test the intercept, and hence fixed bias, is equal to zero. This hypothesis is accepted if the confidence interval for the estimate contains the value 0 in its range. Should this be, it can be concluded that fixed bias is not present. Conversely, if the hypothesis is rejected, then it is concluded that the intercept is non zero, and that fixed bias is present.

Testing for proportional bias is a very similar procedure. The 95% confidence interval for the slope estimate can be used to test the hypothesis that the slope is equal to 1. This hypothesis is accepted if the confidence interval for the estimate contains the value 1 in its range. If the hypothesis is rejected, then it is concluded that the slope is significant different from 1 and that a proportional bias exists.

For convenience, a new data set shall be introduced to demonstrate Deming regression. Measurements of transmitral volumetric flow (MF) by doppler echocardiography, and left ventricular stroke volume (SV) by cross sectional echocardiography in 21 patients with aortic valve disease are tabulated in Zhang et al. (1986). This data set features in the discussion of method comparison studies in Altman (1991, p.398) .

Carroll and Ruppert (1996) states that Deming's regression is acceptable only when the precision ratio (λ, in their paper as η) is correctly specified, but in practice this is often not the case, with the λ being underestimated.

Patient	MF (cm^3)	SV (cm^3)	Patient	MF (cm^3)	SV (cm^3)	Patient	MF (cm^3)	SV (cm^3)
1	47	43	8	75	72	15	90	82
2	66	70	9	79	92	16	100	100
3	68	72	10	81	76	17	104	94
4	69	81	11	85	85	18	105	98
5	70	60	12	87	82	19	112	108
6	70	67	13	87	90	20	120	131
7	73	72	14	87	96	21	132	131

Table 2.8.2: Transmitral volumetric flow(MF) and left ventricular stroke volume (SV) in 21 patients. (Zhang et al 1986)

2.9 Deming Regression

The most commonly known Model II methodology is known as Deming's Regression, (also known an Ordinary Least Product regression). Deming regression is recommended by Cornbleet and Cochrane (1979) as the preferred Model II regression for use in method comparison studies.

Informative analysis for the purposes of method comparison, Deming Regression is a regression technique taking into account uncertainty in both the independent and dependent variables. Demings method always results in one regression fit, regardless of which variable takes the place of the predictor variables.

As with conventional regression methodologies, Deming regression calculates an estimate for both the slope and intercept for the fitted line, and standard errors thereof. Therefore there is sufficient information to carry out hypothesis tests on both estimates, that are informative about presence of fixed and proportional bias.

Deming regression method also calculates a line of best fit for two sets of data. It differs from simple linear regression in that it is derived in a way that factors in for error in the x-axis, as well as the y-axis. The sum of the square of the residuals of

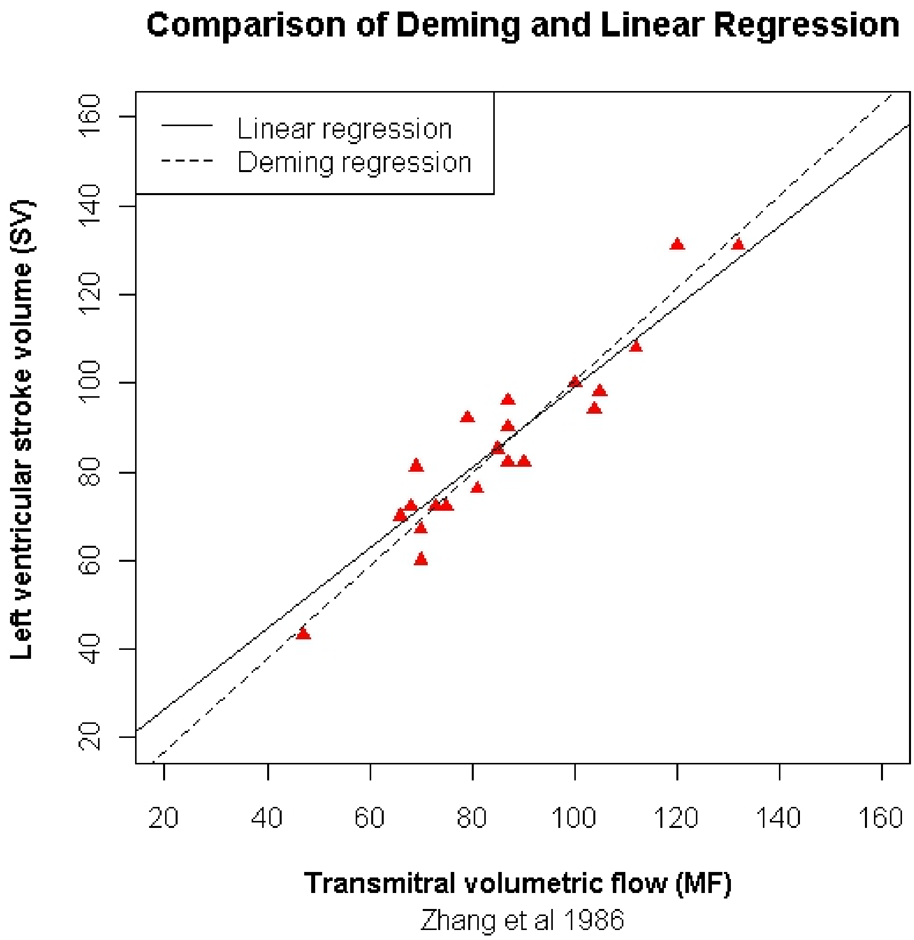

Figure 2.8.1: Deming Regression For Zhang's Data

both variables are simultaneously minimized. This derivation results in the best fit to minimize the sum of the squares of the perpendicular distances from the data points. Normally distributed error of both variables is assumed, as well as a constant level of imprecision throughout the range of measurements.

The sum of squared distances from measured sets of values to the regression line is minimized at an angles specified by the ratio λ of the residual variance of both variables. The measurement error is specified with measurement error variance related as

$$\lambda = \sigma_y^2/\sigma_x^2$$

where σ_x^2 and σ_y^2 is the measurement error variance of the x and y variables, respectively. The variance of the ratio,λ, specifies the angle. When λ is one, the angle is 45 degrees. This approach would be appropriate when errors in y and x are both caused by measurements, and the accuracy of measuring devices or procedures are known. In cases involving only single measurements by each method, λ may be unknown and is therefore assumes a value of one. While this will bias the estimates, it is less biased than ordinary linear regression.

Deming regression assumes that the ratio $\lambda = \sigma_\epsilon^2/\sigma_\eta^2$ is known. In the case where λ is equal to one, (i.e. equal error variances), the methodology is equivalent to ***orthogonal regression***.

2.9.1 Kummel's Estimates

For a given λ, Kummel (1879) derived the following estimate that would later be used for the Deming regression slope parameter. The intercept estimate α is simply estimated in the same way as in conventional linear regression, by using the identity $\bar{Y} - \hat{\beta}\bar{X}$;

$$\hat{\beta} = \frac{S_{yy} - \lambda S_{xx} + [(S_{yy} - \lambda S_{xx})^2 + 4\lambda S_{xy}^2]^{1/2}}{2S_{xy}} \tag{2.5}$$

, with λ as the variance ratio. As stated previously λ is often unknown, and therefore must be assumed to equal one.

Carroll and Ruppert (1996) states that Deming regression is acceptable only when the precision ratio (λ, in their paper as η) is correctly specified, but in practice this is often not the case, with the λ being underestimated. Several candidate models, with varying variance ratios may be fitted, and estimates of the slope and intercept are produced. However no model selection information is available to determine the best fitting model.

As with conventional regression methodologies, Deming regression calculates an estimate for both the slope and intercept for the fitted line, and standard errors thereof. Therefore there is sufficient information to carry out hypothesis tests on both estimates, that are informative about presence of fixed and proportional bias.

2.10 Zhange Example

For convenience, a new data set shall be introduced to demonstrate Deming regression. Measurements of transmitral volumetric flow (MF) by doppler echocardiography, and left ventricular stroke volume (SV) by cross sectional echocardiography in 21 patients with aortic valve disease are tabulated in Zhang et al. (1986). This data set features in the discussion of method comparison studies in Altman (1991, p.398) .

Patient	MF (cm^3)	SV (cm^3)	Patient	MF (cm^3)	SV (cm^3)	Patient	MF (cm^3)	SV (cm^3)
1	47	43	8	75	72	15	90	82
2	66	70	9	79	92	16	100	100
3	68	72	10	81	76	17	104	94
4	69	81	11	85	85	18	105	98
5	70	60	12	87	82	19	112	108
6	70	67	13	87	90	20	120	131
7	73	72	14	87	96	21	132	131

Table 2.10.3: Transmitral volumetric flow(MF) and left ventricular stroke volume (SV) in 21 patients. (Zhang et al 1986)

2.11 Model Evaluation for Deming Regression

Bootstrap techniques can be used to obtain Confidence Intervals for Deming regression estimates. Authors such as Carpenter and Bithell (2000) and Johnson (2001) provide relevant insights.

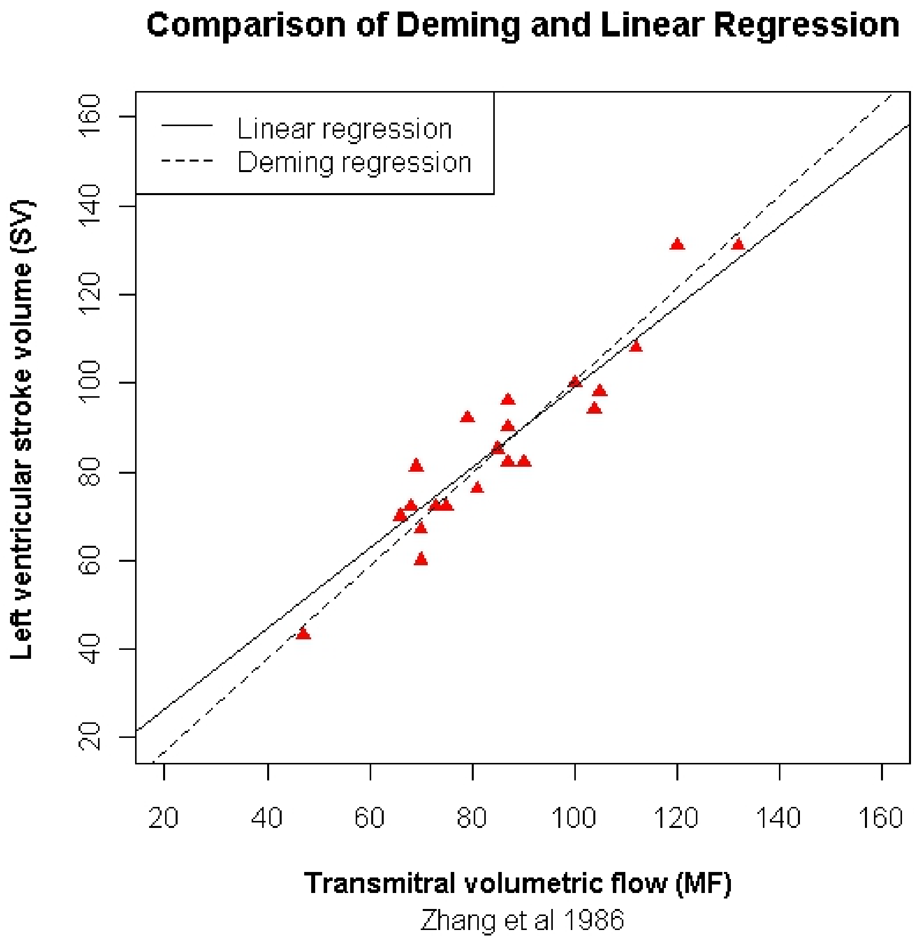

Figure 2.10.2: Deming Regression For Zhang's Data

Model selection and diagnostic technique are well developed for classical linear regression methods. Typically an implementation of a linear model fit will be accompanied by additional information, such as the coefficient of determination and likelihood and information criterions, and a regression ANOVA table. Such additional information has not, as yet, been implemented for Deming regression.

Deming's Regression suffers from some crucial drawbacks. Firstly it is computationally complex, and it requires specific software packages to perform calculations. Secondly, in common with all regression methods, Deming regression is vulnerable to outliers. Lastly, Deming regression is uninformative about the comparative precision of two methods of measurement. Most importantly Carroll and Ruppert (1996) states that Deming's regression is acceptable only when the precision ratio (λ, in their paper as η) is correctly specified, but in practice this is often not the case, with the λ being underestimated. This underestimation leads to an overcorrection for attenuation.

2.12 Other Proposals for Formal Testing

Kinsella (1986) notes the lack of formal testing offered by this Bland-Altman plot. Furthermore, Kinsella (1986) formulates a model for single measurement observations as a linear mixed effects model, i.e. a model that additively combines fixed effects and random effects:

$$Y_{ij} = \quad \mu + \beta_j + u_i + \epsilon_{ij} \qquad i = 1, \dots, n \qquad j = 1, 2$$

The true value of the measurement is represented by μ while the fixed effect due to method j is β_j. For simplicity these terms can be combined into single terms; $\mu_1 = \mu + \beta_1$ and $\mu_2 = \mu + \beta_2$. The inter-method bias is the difference of the two fixed effect terms, $\beta_1 - \beta_2$. Each individual is assumed to give rise to a random error, represented by u_i. This random effects term is assumed to have mean zero and be normally distributed with variance σ^2. There is assumed to be an attendant error for each measurement on each individual, denoted ϵ_{ij}. This is also assumed to have mean zero. The variance of measurement error for both methods are not assumed to be identical for both methods variance, hence it is denoted σ^2_j. The set of observations (x_i, y_i) by methods X and Y are assumed to follow a bivariate normal distribution with expected values $E(x_i) = \mu_i$ and $E(y_i) = \tau_i$ respectively. The variance covariance of the observations $\boldsymbol{\Sigma}$ is given by

$$\boldsymbol{\Sigma} = \begin{bmatrix} \sigma^2 + \sigma^2_1 & \sigma^2 \\ \sigma^2 & \sigma^2 + \sigma^2_2 \end{bmatrix}$$

Kinsella (1986) demonstrates the estimation of the variance terms and relative precisions relevant to a method comparison study, with attendant confidence intervals for both. The measurement model introduced by Grubbs (1948, 1973) provides a formal procedure for estimating the variances σ^2, σ_1^2 and σ_2^2. Grubbs (1948) offers estimates, commonly known as Grubbs estimators, for the various variance components. These estimates are maximum likelihood estimates, which shall be revisited in due course.

$$\hat{\sigma^2} = \sum \frac{(x_i - \bar{x})(y_i - \bar{y})}{n-1} = Sxy$$
$$\hat{\sigma_1^2} = \sum \frac{(x_i - \bar{x})^2}{n-1} = S^2x - Sxy$$
$$\hat{\sigma_2^2} = \sum \frac{(y_i - \bar{y})^2}{n-1} = S^2y - Sxy$$

Thompson (1963) defines $\Delta_j = \sigma^2/\sigma_j^2, j = 1, 2$, to be a measure of the relative precision of the measurement methods, and demonstrates how to make statistical inferences about Δ_j. Based on the following identities,

$$\begin{aligned} C_x &= (n-1)S_x^2, \\ C_{xy} &= (n-1)S_{xy}, \\ C_y &= (n-1)S_y^2, \\ |A| &= C_x \times C_y - (C_{xy})^2, \end{aligned}$$

the confidence interval limits of Δ_1 are

$$\frac{C_{xy} - t(\frac{|A|}{n-2})^{\frac{1}{2}}}{C_x - C_{xy} + t(\frac{|A|}{n-2})^{\frac{1}{2}}} < \Delta_1 < \frac{C_{xy} + t(\frac{|A|}{n-2})^{\frac{1}{2}}}{C_x - C_{xy} - t(\frac{|A|}{n-1})^{\frac{1}{2}}}$$

The value t is the $100(1-\alpha/2)\%$ upper quantile of Student's t distribution with $n-2$ degrees of freedom (Kinsella, 1986). The confidence limits for Δ_2 are found by substituting C_y for C_x in (1.2). Negative lower limits are replaced by the value 0.

The case-wise differences and means are calculated as $d_i = x_i - y_i$ and $a_i = (x_i + y_i)/2$ respectively. Both d_i and a_i are assumed to follow a bivariate normal distribution with $E(d_i) = \mu_d = \mu_1 - \mu_2$ and $E(a_i) = \mu_a = (\mu_1 + \mu_2)/2$, and the variance matrix $\Sigma_{(a,d)}$ is

$$\Sigma_{(a,d)} = \begin{bmatrix} \sigma_1^2 + \sigma_2^2 & \frac{1}{2}(\sigma_1^2 - \sigma_2^2) \\ \frac{1}{2}(\sigma_1^2 - \sigma_2^2) & \sigma^2 + \frac{1}{4}(\sigma_1^2 + \sigma_2^2) \end{bmatrix}. \tag{2.6}$$

2.13 Structural Equation Modelling

Structural Equation modelling is a statistical technique used for testing and estimating causal relationships using a combination of statistical data and qualitative causal assumptions.(Carrasco, 2004) describes the structural equation model is a regression approach that allows to estimate a linear regression when independent variables are measured with error . The Structural equations approach avoids the biased estimation of the slope and intercept that occurs in ordinary least square regression.

Several authors, such as Lewis et al. (1991), Kelly (1985),Voelkel and Siskowski (2005a) and Hopkins (2004) advocate the use of SEM methods for method comparison. In Hopkins (2004), a critique of the Bland-Altman plot he makes the following remark:

What's needed for a comparison of two or more measures is a generic approach more powerful even than regression to model the relationship and error structure of each measure with a latent variable representing the true value.

Hopkins also adds that he himself is collaborating in research utilising SEM and Mixed Effects modelling. Kelly (1985) advised that *the Structural equations model is used to estimate the linear relationship between new and standards method. The Delta method is used to find the variance of the estimated parameters*(Kelly, 1985).

However Bland and Altman (1987) contends that it is unnecessary to perform elaborate statistical analysis, while also criticizing the SEM approach on the basis that it offers insights on inter-method bias only, and not the variability about the line of equality.

> *However, it is quite wrong to argue solely from a lack of bias that two methods can be regarded as comparable... Knowing the data are consistent with a structural equation with a slope of 1 says something about the absence of bias but nothing about the variability about $Y = X$ (the difference between the measurements), which, as has already been stated, is all that really matters.*

2.14 Other Types of Studies / Gold Standards

? categorize method comparison studies into three different types. The key difference between the first two is whether or not a 'gold standard' method is used. In situations where one instrument or method is known to be 'accurate and precise', it is considered as the'gold standard' (**?**). A method that is not considered to be a gold standard is referred to as an 'approximate method'. In calibration studies they are referred to a criterion methods and test methods respectively.

1. Calibration problems. The purpose is to establish a relationship between methods, one of which is an approximate method, the other a gold standard. The results of the approximate method can be mapped to a known probability distribution of the results of the gold standard (**?**). (In such studies, the gold standard method and corresponding approximate method are generally referred to a criterion method and test method respectively.) Altman and Bland (1983) make clear that their methodology is not intended for calibration problems.

2. Comparison problems. When two approximate methods, that use the same units of measurement, are to be compared. This is the case which the Bland-Altman methodology is specfically intended for, and therefore it is the most relevant of the three.

3. Conversion problems. When two approximate methods, that use different units of measurement, are to be compared. This situation would arise when the measurement methods use 'different proxies', i.e different mechanisms of measurement. **?** deals specifically with this issue. In the context of this study, it is the least relevant of the three.

Dunn (2002, p.47) cautions that'gold standards' should not be assumed to be error free. 'It is of necessity a subjective decision when we come to decide that a particular method or instrument can be treated as if it was a gold standard'. The clinician gold standard , the sphygmomanometer, is used as an example thereof. The sphygmomanometer ‘leaves considerable room for improvement’ (Dunn, 2002). Pizzi (1999) similarly addresses the issue of glod standards, ‘well-established gold standard may itself be imprecise or even unreliable’.

The NIST F1 Caesium fountain atomic clock is considered to be the gold standard when measuring time, and is the primary time and frequency standard for the United States. The NIST F1 is accurate to within one second per 60 million years (NIST, 2009).

Measurements of the interior of the human body are, by definition, invasive medical procedures. The design of method must balance the need for accuracy of measurement with the well-being of the patient. This will inevitably lead to the measurement error as described by Dunn (2002). The magnetic resonance angiogram, used to measure internal anatomy, is considered to the gold standard for measuring aortic dissection. Medical test based upon the angiogram is reported to have a false positive reporting rate of 5% and a false negative reporting rate of 8%. This is reported as sensitivity of 95% and a specificity of 92% (ACR, 2008).

In literature they are, perhaps more accurately, referred to as ‘fuzzy gold standards’ (Phelps and Hutson, 1995). Consequently when one of the methods is essentially a fuzzy gold standard, as opposed to a ‘true’ gold standard, the comparison of the criterion and test methods should be consider in the context of a comparison study, as well as of a calibration study.

2.15 Bland Altman plots using ’Gold Standard’ raters

According to Bland and Altman, one should use the methodology previous outlined, even when one of the raters is a Gold Standard.

Structural Equation Modelling

Authors, such as a **?**, **?** and Voelkel and Siskowski (2005b), strongly advocate the use of *Structural Equation Models* for the purposes of method comparison. Conversely Bland and Altman (1999) also states that consider structural equation models to be inappropriate.

Chapter 3

Error In Variable Models

3.1 Background

In method comparison studies, it is of importance to assure that the presence of a difference of medical importance is detected. For a given difference, the necessary number of samples depends on the range of values and the analytical standard deviations of the methods involved. For typical examples, the present study evaluates the statistical power of least-squares and Deming regression analyses applied to the method comparison data.

3.2 Model I and II Regression

On account of the fact that one set of measurements are linearly related to another, one could surmise that Linear Regression is the most suitable approach to analyzing comparisons. This approach is unsuitable on two counts. Firstly one of the assumptions of Regression analysis is that the independent variable values are without error.

In method comparison studies one must assume the opposite; that there is error present in the measurements. Secondly a regression of X on Y would yield and entirely different result from Y on X.

Model I regression is unsuitable for method comparison studies. Even in the case where one method is a gold standard , it is disputed as to whether it is a valid approach.

Model II regression is suitable for method comparison studies, but it is more difficult to execute. Both Model I and II regression models are unduly influenced by outliers.

Cornbleet and Cochrane (1979) argue for the use of methods that based on the assumption that both methods are imprecisely measured ,and that yield a fitting that is consistent with both 'X on Y' and 'Y on X' formulations. These methods uses alternatives to the OLS approach to determine the slope and intercept.

They describe three such alternative methods of regression; Deming, Mandel, and Bartlett regression. Collectively the authors refer to these approaches as Model II regression techniques.

- The authors make the distinction between model I and model II regression types.
- Model II regression is the appropriate type when the predictor variable x is measured with imprecision. Cornbleet and Cochrane remark that clinical laboratory measurements usually increase in absolute imprecision when larger values are measured.
- Model II regression is the appropriate type when the predictor variable x is measured with imprecision. Cornbleet and Cochrane remark that clinical laboratory measurements usually increase in absolute imprecision when larger values are measured.

3.2.1 Model I regression [Criterion v Test]

Cornbleet and Cochrane (1979) define this analysis as the case in which the independent variable, X, is measured without error, with y as the dependent variable.

Simple Linear Regression is well known statistical technique, wherein estimates for slope and intercept of the line of best fit are derived according to the Ordinary Least Square (OLS) principle. This method is known to Cornbleet and Cochrane (1979) as Model I regression.

Simple linear regression is defined as such with the name 'Model I regression' by Cornbleet and Cochrane (1979), in contrast to 'Model II regression'.

3.2.2 Model II regression [Test V Test]

In this type of analysis, both of the measurement methods are test methods, with both expected to be subject to error. Deming regression is an approach to model II regression.

In Model I regression, the independent variable is assumed to be measured without error. For method comparison studies, both sets of measurement must be assumed to be measured with imprecision and neither case can be taken to be a reference method. Arbitrarily selecting either method as the reference will yield two conflicting outcomes. A fitting based on 'X on Y' will give inconsistent results with a fitting based on 'Y on X'. Consequently model I regression is inappropriate for such cases.

Simple linear regression calculates a line of best fit for two sets of data, n which the independent variable, X, is measured without error, with y as the dependent variable.

SLR (Model I) regression is considered by many Altman and Bland (1983); Cornbleet and Cochrane (1979); Ludbrook (1997) to be wholly unsuitable for method comparison studies, although recommended for use in calibration studies [Corncoch]. Even in the case where one method is a gold standard , it is disputed as to whether it is a valid approach. Model II regression is more suitable for method comparison studies, but it is more difficult to execute. Both Model I and II regression models are unduly influenced by outliers. Regression Models can not be used to analyze repeated measurements

Conversely, Cornbleet and Cochrane (1979) state that when the independent variable X is a precisely measured reference method, Model I regression may be considered suitable. They qualify this statement by referring the X as *the correct value*, tacitly implying that there must still be some measurement error present. The validity of this approach has been disputed elsewhere.

This regression method also calculates a line of best fit for two sets of data. It differs from Model I regression in that it is derived in a way that factors in for error in the x-axis, as well as the y-axis. Cornbleet and Cochrane (1979) refer to it as 'Model II regression'.

Model II regression method also calculates a line of best fit for two sets of data. It differs from Model I regression in that it is derived in a way that factors in for error in the x-axis, as well as the y-axis. Cornbleet and Cochrane (1979) refer to it as 'Model II regression'.

- Model II regression [Test V Test] In this type of analysis, both of the measurement methods are test methods, with both expected to be subject to error. Deming regression is an approach to model II regression.

- Model I regression [Criterion v Test] Cornbleet and Cochrane (1979) define this analysis as the case in which the independent variable, X, is measured without error, with Y as the dependent variable.

- In method comparison studies, the X variable is a precisely measured reference method. In the Cornbleet and Cochrane (1979) paper It is argued that criterion may be regarded as the correct value. Other papers dispute this.

3.2.3 Contention

Several papers have commented that this approach is undermined when the basic assumptions underlying linear regression are not met, the regression equation, and consequently the estimations of bias are undermined. Outliers are a source of error in regression estimates.

In method comparison studies, the X variable is a precisely measured reference method. In the Cornbleet and Cochrane (1979) paper. It is argued that criterion may be regarded as the correct value. Other papers dispute this.

3.3 Deming Regression

The appropriate estimates were derived by Kummel (1879), but were popularized in the context of medical statistics and clinical chemistry by Deming (1943).

3.4 Error-In-Variable Models for Regression

3.4.1 Compuational Aspects of Deming Regression

As stated previously, the fundamental flaw of simple linear regression is that it allows for measurement error in one variable only. This causes a downward biased slope estimate.

3.4.2 Variance Ratio

The Deming regression line is estimated by minimizing the sums of squared deviations in both the x and y directions at an angle determined by the ratio of the analytical standard deviations for the two methods.

In cases involving only single measurements by each method, λ may be unknown and is therefore assumes a value of one. While this will bias the estimates, it is less biased than ordinary linear regression.

This ratio can be estimated if multiple measurements were taken with each method, but if only one measurement was taken with each method, it can be assumed to be equal to one.

3.4.3 Estimating the Variance ratio

In cases involving only single measurements by each method, λ may be unknown and is therefore assumes a value of one. While this will bias the estimates, it is less biased than ordinary linear regression.

$$
x_i = \mu + \beta_0 + \epsilon_{xi}
$$
$$
y_i = \mu + \beta_1 + \epsilon_{yi}
$$

The inter-method bias is the difference of these biases. In order to determine an estimate for the residual variances, one of the method biases must be assumed to be zero, i.e. $\beta_0 = 0$. The inter-method bias is now represented by β_1.

$$
\begin{aligned}
x_i &= \mu + \epsilon_{xi} \\
y_i &= \mu + \beta_1 + \epsilon_{yi}
\end{aligned}
$$

The residuals can be expressed as

$$
\begin{aligned}
\epsilon_{xi} &= x_i - \mu \\
\epsilon_{yi} &= y_i - (\mu + \beta_1)
\end{aligned}
$$

The variance of the residuals are equivalent to the variance of the corresponding observations, $\sigma^2_{\epsilon x} = \sigma^2_x$ and $\sigma^2_{\epsilon y} = \sigma^2_y$.

$$
\lambda = \frac{\sigma^2_{yx}}{\sigma^2_y}. \tag{3.1}
$$

Assuming constant standard deviations, and given duplicate measurements, the analytical standard deviations are given by

$$
SD^2_{ax} = \frac{1}{2n} \sum (x_{2i} - x_{1i})^2
$$
$$
SD^2_{ay} = \frac{1}{2n} \sum (y_{2i} - y_{1i})^2
$$

Using duplicate measurements, one can estimate the analytical standard deviations and compute their ratio. This ratio is then used for computing the slope by the Deming method.[Linnet]

3.4.4 Inferences for Deming Regression

The Intercept and Slope are calculated according to Combleet & Gochman, 1979. The standard errors and confidence intervals are estimated using the jackknife method (Armitage et al., 2002).

The 95% confidence interval for the Intercept can be used to test the hypothesis that A=0. This hypothesis is accepted if the confidence interval for A contains the value 0. If the hypothesis is rejected, then it is concluded that A is significantly different from 0 and both methods differ at least by a constant amount.

The 95% confidence interval for the Slope can be used to test the hypothesis that B=1. This hypothesis is accepted if the confidence interval for B contains the value 1. If the hypothesis is rejected, then it is concluded that B is significantly different from 1 and there is at least a proportional difference between the two methods.

3.4.5 Expaning the use of Deming Regression for MCS

As noted before, Deming regression is an important and informative methodology in method comparison studies. For single measurement method comparisons, Deming regression offers a useful complement to LME models.

3.5 Performance in the presence of outliers

All least square estimation methods are sensitive to outliers. In common with all regression methods, Deming regression is vulnerable to outliers.

Bland Altman's 1986 paper contains a data set, measurement of mean velocity of circumferential fibre shortening (VCF) by the long axis and short axis in M-mode echocardiography. Evident in this data set are outliers. Choosing the most noticeable, we shall use the deming regression method on this data set, both with and without this outlier, to assess its influence.

- In the presence of the outlier, the intercept and slope are estimated to be -0.0297027 and 1.0172959 respectively.
- Without the outlier the intercept and slope are estimated to be -0.11482220 and 1.09263112 respectively.
- We therefore conclude that Deming Regression is adversely affected by outliers , in the same way model I regression is.

3.6 Using LME models to estimate the ratio (BXC)

$$y_{mi} = \mu + \beta_m + b_i + \epsilon_{mi}$$

with β_m is a fixed effect for the method m and b_i is a random effect associated with patient i, and ϵ_{mi} as the measurement error. This is a simple single level LME model. Pinheiro and Bates (1994) provides for the implementation of fitting a model. The variance ratio of the residual variances is immediately determinable from the output. This variance ratio can be use to fit a Deming regression, as described in chapter 1.

3.7 Implementations

Thus far, one of the few `R` implementations of Deming regression is contained in the 'MethComp' package. (Carstensen et al., 2008).

Unless specified otherwise, the variance ratio λ has a default value of one. A means of computing likelihood functions would potentially allow for an algorithm for estimating the true variance ratio.

3.8 Weighted Deming Regression

Weighted linear regression allows for non-constancy of the standard deviation of the y variable. However it is assumed that X is without measurement error. Weighted Deming regression takes into account the non-constant proportional measurement errors in both variables.Despite the non-constancy, it is necessary to retain the constant value of λ.

In **both forms** of Deming regression, λ is assumed to be constant through out the range of measurements. For WDR weights w_i are used to compute the sums of squares and cross products. The weights are inversely proportional to the squared analytical variance at any given value.

3.9 Koning

`Use of deming regression in method comparison studies.`

`Henk Konings`

Accuracy is closeness to the true value, or alternatively, having a low measurement error.

The determination of a true value for a biological specimen is difficult and sometimes impossible.

Precision is expressed in terms of standard deviation, coefficient of variance or variance.

In Deming regression, the errors between methods are assigned to both methods in proportion to the variances of the methods.

3.10 Linnet - References

The statistical procedures are described in: Linnet K. Necessary sample size for method comparison studies based on regression analysis. Clin Chem 1999; 45: 882-94. Linnet

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3.11 Ordinary Least Product Regression

Ludbrook (1997) states that the grouping structure can be straightforward, but there are more complex data sets that have a hierarchical(nested) model.

Observations between groups are independent, but observations within each groups are dependent because they belong to the same subpopulation. Therefore there are two sources of variation: between-group and within-group variance.

3.12 Least Products Regression

Used as an alternative to Bland-Altman Analysis, this method is also known as 'Geometric Mean Regression' and 'Reduced Major Axis Regression'. This regression model minimizes the areas of the right triangles formed by the data points' vertical and horizontal deviations from the fitted line and the fitted line.

Model II regression analysis caters for cases in which random error is attached to both dependent and independent variables. Comparing methods of measurement is just such a case.(Ludbrook)

Least products regression is the reviewer's preferred technique for analysing the Model II case. In this, the sum of the products of the vertical and horizontal deviations of the x,y values from the line is minimized.

Least products regression analysis is suitable for calibrating one method against another. It is also a sensitive technique for detecting and distinguishing fixed and proportional bias between methods.

Least-products regression can lead to inflated SEEs and estimates that do not tend to their true values an N approaches infinity (Draper and Smith, 1998).

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