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Chapter 1

Formal Models and Tests

1.1 Formal Models and Tests

While the Bland-Altman plot is a simple technique for comparing measurements, Kinsella (1986) noted the lack of formal testing offered by that approach, with it relying on the practitioner's opinion to judge the outcome. Altman and Bland (1983) proposed a formal test on the Pearson correlation coefficient of case-wise differences and means which, according to the authors, is equivalent to the 'Pitman-Morgan Test', a key contribution to method comparison studies that shall be discussed shortly (Morgan, 1939; Pitman, 1939). 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) remarked that '*we do not see a place for methods of analysis based on hypothesis testing*', while also stating that they consider structural equation models to be inappropriate.

1.1.1 Kinsella's Model

Kinsella (1986) presented a simple model to describe a measurement by each method, describing the relationship with its real value. Only the non-replicate case is considered, as this is the context of the Bland-Altman plots. Other authors, such as Carstensen

(2004); Carstensen et al. (2008), present similar formulations of the same model, as well as modified models to account for multiple measurements by each methods on each item, known as replicate measurements.

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.

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

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, $\mu_d = \beta_1 - \beta_2$. Each of the i items are assumed to give rise to random error, represented by u_i . This random effects terms 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 item, denoted ϵ_{ij} , which 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_j^2 . The set of observations (x_i, y_i) by methods X and Y are assumed to follow the bivariate normal distribution with expected values $E(x_i) = \mu_1$ and $E(y_i) = \mu_2$ respectively. The variance covariance of the observations Σ is given by

$$\Sigma_{(X,Y)} = \begin{bmatrix} \sigma^2 + \sigma_1^2 & \sigma^2 \\ \sigma^2 & \sigma^2 + \sigma_2^2 \end{bmatrix}.$$

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 $E(a_i) = \mu_a = (\mu_1 + \mu_2)/2$. Constructively, the paired measurements can be expressed as

$$d_i = x_i - y_i \sim \mathcal{N}(\mu_d, \sigma_1^2 + \sigma_2^2).$$

The variance matrix $\Sigma_{(A,D)}$ is

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

In some types of analysis, such as the conversion problems described by Lewis et al. (1991), measurements made by methods X and Y may be denominated in different units, and an estimate for the proportionality, i.e. a scaling factor, must be determined. Using amended notation, for comparing two methods X and Y , for the measurement of item i is formulated as

$$X_i = \tau_i + \epsilon_{i1}, \quad \epsilon_{i1} \sim \mathcal{N}(0, \sigma_1^2), \quad (1.2)$$

$$Y_i = \alpha + \lambda\tau_i + \epsilon_{i2}, \quad \epsilon_{i2} \sim \mathcal{N}(0, \sigma_2^2). \quad (1.3)$$

Here the unknown ‘true value’ is τ_i , α represents the inter-method bias, and the scaling factor is denoted here as λ . For the time being, we will restrict ourselves to problems where λ is assumed to be 1, but will revert back to this conversion problem later.

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 estimate the variances σ^2 , σ_1^2 and σ_2^2 devices. Grubbs (1948) offers maximum likelihood estimates, commonly known as Grubbs estimators, for the various variance components,

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

Thompson (1963) presents confidence intervals for the relative precisions of the measurement methods, $\Delta_j = \sigma_S^2/\sigma_j^2$ (where $j = 1, 2$), as well as the variances σ_S^2, σ_1^2 and σ_2^2 ,

$$\Delta_1 > \frac{C_{xy} - t(|A|/n-2))^{\frac{1}{2}}}{C_x - C_{xy} + t(|A|/n-2))^{\frac{1}{2}}}. \quad (1.4)$$

Thompson (1963) defines Δ_j to be a measure of the relative precision of the measurement methods, with $\Delta_j = \sigma^2/\sigma_j^2$. Thompson also 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

$$\Delta_1 < \frac{C_{xy} - t(\frac{|A|}{n-2})^{\frac{1}{2}}}{C_x - C_{xy} + t(\frac{|A|}{n-2})^{\frac{1}{2}}} \quad (1.5)$$

$$\Delta_1 > \frac{C_{xy} + t(\frac{|A|}{n-2})^{\frac{1}{2}}}{C_x - C_{xy} - t(\frac{|A|}{n-2})^{\frac{1}{2}}} \quad (1.6)$$

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 1.5 and 1.6. Negative lower limits are replaced by the value 0.

1.1.2 Pitman-Morgan Testing

An early contribution to formal testing in method comparison was devised concurrently by Pitman (1939) and Morgan (1939) in separate contributions.

The classical Pitman-Morgan test can be adapted as a hypothesis test of equal variance for both methods, based on the correlation value between differences and means $\rho_{a,d}$. This is a test statistic for the null hypothesis of equal variances given bivariate normality ;

$$\rho(a, d) = \frac{\sigma_1^2 - \sigma_2^2}{\sqrt{(\sigma_1^2 + \sigma_2^2)(4\sigma_S^2 + \sigma_1^2 + \sigma_2^2)}}. \quad (1.7)$$

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

Bartko (1994) describes the Pitman-Morgan test as identical to the test of the slope equal to zero in the regression of Y_{i1} on Y_{i2} , a result that can be derived using straightforward algebra. The Pitman-Morgan test is equivalent to the marginal test of the slope estimate in Bradley and Blackwood (1989).

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. Only if the two methods show comparable precision then the paired sample t -test is appropriate for testing the inter-method bias. Therefore, it should only be used in succession to the Pitman-Morgan test. Furthermore, these tests are only valid in the case of non-replicate measurements.

1.1.3 Regression-Based Testing Techniques

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 two paired data sets.

Bradley and Blackwood (1989) construct a linear model which fits D on S , which are the case-wise differences and sums of a pair of measurements respectively, creating estimates for intercept and slope, β_0 and β_1 :

$$D = \beta_0 + \beta_1 S.$$

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 $\beta_0 = \beta_1 = 0$). The test is conducted using an F -test, calculated from the results of the regression of D on S . Bartko (1994) amends this approach for use in method comparison studies, using the averages of the pairs, as opposed to the

sums. This approach can facilitate simultaneous usage of test with the Bland-Altman technique.

Bartko's test statistic is then calculated from the regression analysis of variance values (Bradley and Blackwood, 1989) and is distributed as ' F ' random variable:

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

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.

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.

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

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.

1.2 Regression-Based 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 these 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. Additionally one method must be arbitrarily identified as the independent variable.

Cornbleet and Cochrane (1979) argue for the use of alternatives to the OLS approach, 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.

Errors-in-variables models assume the presence of error in both variables X and Y have been proposed for use instead (Cornbleet and Cochrane, 1979; Ludbrook, 1997). These models are collectively known as ‘Model II regression’. These approaches suitable for method comparison studies, but are more difficult to implement.

1.2.1 Deming Regression

The most commonly known Model II methodology is known as Deming’s Regression, and is recommended by Cornbleet and Cochrane (1979) as the preferred Model II regression for use in method comparison studies. The Bland-Altman plot is uninformative about the comparative influence of proportional bias and fixed bias. However Deming regression can provide independent tests for both types of bias.

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 Deming regression method calculates a line of best fit for two sets of data. This derivation results in the best fit to simultaneously minimize the sum of the squares of the perpendicular distances from the data points at an angle specified by the ratio λ . For OLS Models, the distances are minimized in the vertical direction (Linnet, 1999). When λ is one, the angle is 45 degrees. Normally distributed error of both variables is assumed, as well as a constant level of imprecision throughout the range of measurements.

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

1.2.2 Kummel's Estimates

The appropriate estimates were derived by Kummel (1879), but were popularized in the context of medical statistics and clinical chemistry by Deming (1943). For a given λ , Kummel (1879) derived the following estimate that would later be used for the Deming regression slope parameter.

$$\hat{\beta} = \frac{S_{yy} - \lambda S_{xx} + [(S_{yy} - \lambda S_{xx})^2 + 4\lambda S_{xy}^2]^{1/2}}{2S_{xy}}, \quad (1.8)$$

with λ as the variance ratio. The intercept estimate α is simply estimated in the same way as in conventional linear regression, by using the identity $\bar{Y} - \hat{\beta}\bar{X}$.

This approach would be appropriate when errors in y and x are both caused by measurements, and the accuracy of measurement systems are known. In cases involving only single measurements by each method, λ may be unknown and is therefore assumed a value of one. While this will bias the estimates, it is less biased than ordinary linear regression. Deming regression assumes that the variance ratio λ is known. When λ is defined as one, (i.e. equal error variances), the approach is known as orthogonal regression. 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.

1.2.3 Inferences for Deming Regression

As with classical regression models, Deming regression calculates an estimate for both the slope and intercept for the fitted line, and standard errors thereof Cornbleet and Cochrane (1979). Standard errors and confidence intervals can be estimated using the Bootstrap techniques. Authors such as Carpenter and Bithell (2000) and Johnson (2001) provide relevant insights.

Therefore there is sufficient information to carry out hypothesis tests on both estimates, that are informative about presence of constant and proportional bias. The test for the intercept estimate acts as a test for the presence of constant bias between both measurement methods. Similarly the test for the slope estimate can be used to formally test proportional bias between the two methods.

One of the assumptions that underline Deming regression is constancy of the measurement errors throughout the range of values. However the author point out that *clinical laboratory measurements usually increase in absolute imprecision when larger values are measured.*

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.

1.2.4 Worked Example of Deming Regression

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).

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.

Deming regression is undermined by several factors. 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

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

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.

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 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.

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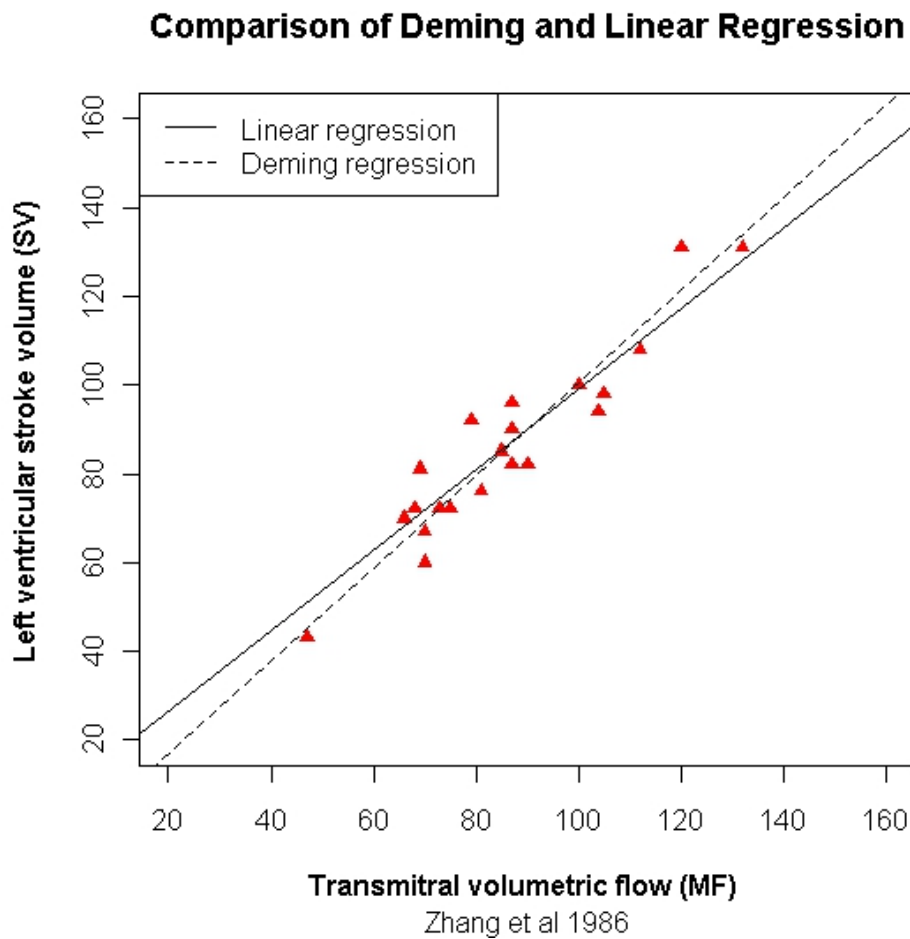


Figure 1.2.1: Deming Regression For Zhang’s Data

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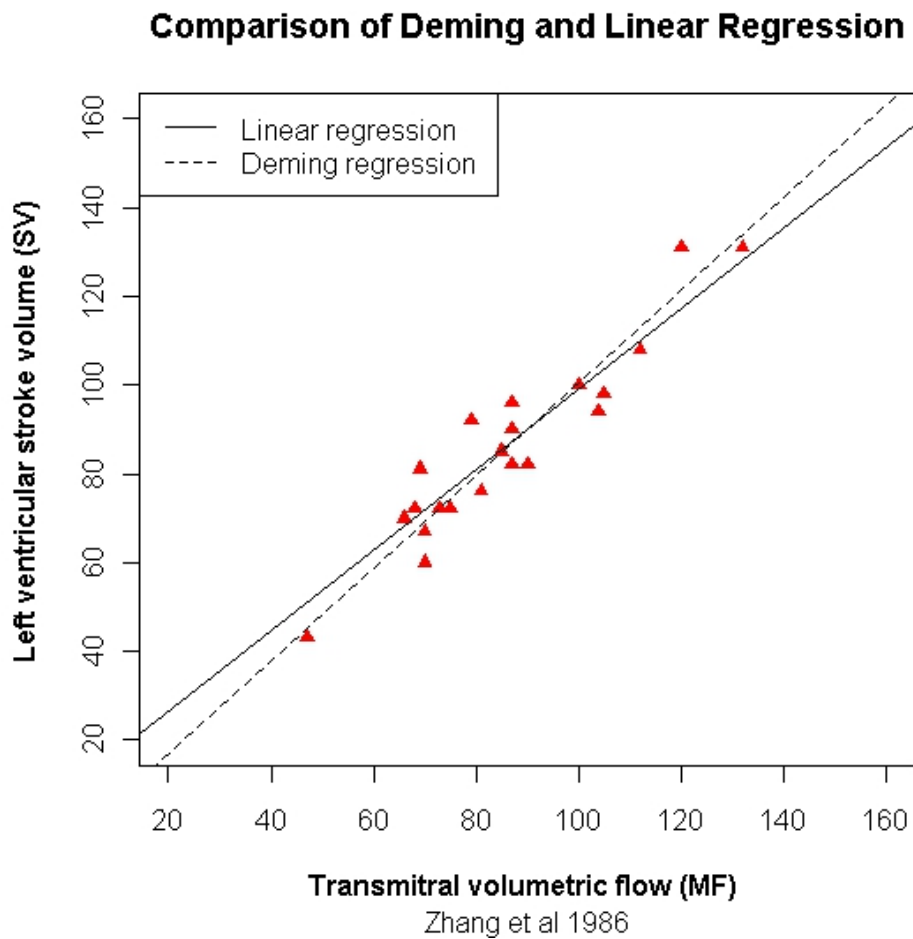


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As noted before, Deming regression is an important and informative methodology in method comparison studies. For single measurement method comparisons, Deming regression offers a useful complement to LME models.

1.4 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 (2005) 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).

Conversely Bland and Altman (1999) also states that consider structural equation models to be inappropriate. However Altman et al. (1987) contends that it is unneces-

sary 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.

Dunn (2002) highlights an important issue regarding using models such as structural equation modelling; 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, the ratio of the precision of both methods $\lambda = \frac{\sigma_1^2}{\sigma_2^2}$ must often be assumed to be equal to 1 (Linnet, 1998).

Dunn (2002) considers techniques based on two methods with single measurements on each subject as inadequate for a serious study on the measurement characteristics of the methods, simply 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 an invasive medical procedure.

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Dunn (2002) considers techniques based on two methods with single measurements on each subject as inadequate for a serious study on the measurement characteristics of the methods, simply 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 an invasive medical procedure.

1.6 Model for Replicate Measurements

The single measurement model can be generalized to the replicate measurement case, by additionally specifying replicate values. Let y_{mir} be the r -th replicate measurement for item i made by method m . Further to Barnhart et al. (2007) fixed effect can be expressed with a single term α_{mi} , which incorporate the true value μ_i .

$$y_{mir} = \mu_i + \alpha_m + e_{mir}$$

Combining fixed effects (Barnhart et al., 2007), we write,

$$y_{mir} = \alpha_{mi} + e_{mir}.$$

The following assumptions are required e_{mir} is independent of the fixed effects with mean $E(e_{mir}) = 0$. Further to Barnhart et al. (2007) between-item and within-item variances $\text{Var}(\alpha_{mi}) = \sigma_{Bm}^2$ and $\text{Var}(e_{mir}) = \sigma_{Wm}^2$

1.6.1 Carstensen's 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 r th replicate measurement on the i th item by the m th method ($m = 1, 2$, $i = 1, \dots, N$, and $r = 1, \dots, n$), can be written as

$$y_{mir} = \alpha_m + \mu_i + a_{ir} + c_{mi} + \epsilon_{mir}. \quad (1.10)$$

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 $\epsilon_{mir} \sim \mathcal{N}(0, \varphi_m^2)$. 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.

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.

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir}, \quad e_{mi} \sim \mathcal{N}(0, \sigma_m^2), \quad c_{mi} \sim \mathcal{N}(0, \tau_m^2). \quad (1.11)$$

Based on this model, Carstensen et al. (2008) compute the limits of agreement as

$$\alpha_1 - \alpha_2 \pm 2\sqrt{\tau_1^2 + \tau_2^2 + \varphi_1^2 + \varphi_2^2}. \quad (1.12)$$

This provides the basis of a modified approach to computing LOAs that will be reverted to later.

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