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# Chapter 1

## LOAS

### 1.1 Calculation of limits of agreement

Carstensen et al. (2008) computes the limits of agreement to the case with repeated measurements by using LME models.

Roy (2009b) formulates a very powerful method of assessing whether two methods of measurement, with replicate measurements, also using LME models. Roy's approach is based on the construction of variance-covariance matrices.

Importantly, Roy's approach does not address the issue of limits of agreement (though another related analysis, the coefficient of repeatability, is mentioned).

This paper seeks to use Roy's approach to estimate the limits of agreement. These estimates will be compared to estimates computed under Carstensen's formulation.

### 1.2 Carstensen Intro

Carstensen et al. (2008) also use a LME model for the purpose of comparing two methods of measurement where replicate measurements are available on each item. Their interest lies in generalizing the popular limits-of-agreement (LOA) methodology advocated by Bland and Altman (1986) to take proper cognizance of the replicate measurements.

Bendix Carstensen et al. proposed the use of LME models to allow for a more statistically rigorous approach to computing Limits of Agreement. The respective papers also discuss several shortcomings for techniques for dealing with replicate measurements, as proposed by Bland-Altman 1999.

Carstensen et al. (2008) sets out a methodology of computing the limits of agreement based upon variance component estimates derived using linear mixed effects models. Measures of repeatability, a characteristic of individual methods of measurements, are also derived using this method.

Carstensen et al. (2008) proposes an approach for comparing two or more methods of measurement based on linear mixed effects models. This approach extends the well established Bland-Altman methodology for the case of replicate measurements on each item. Carstensen considers the matter of computing an appropriate estimate for the standard deviation of case-wise differences, so as to determine the limits of agreement. As the interest lies in extending the Bland-Altman methodology, other formal tests are not described.

Carstensen et al. (2008) also presents a methodology to compute the limits of agreement based on LME models. The method of computation is similar to Roy's model, but for absence of the covariance estimates. In cases where there is negligible covariance between methods, the limits of agreement computed using Roy's model accord with those computed using model described by (1.17). In cases where some degree of covariance is present between the two methods, the limits of agreement computed using models will differ. In the presented example, it is shown that Roy's LOAs are lower than those of (1.17), when covariance between methods is present.

Importantly, Carstensen's underlying model differs from Roy's model in some key respects, and therefore a prior discussion of Carstensen's model is required. Carstensen et al. (2008) presents a methodology to compute the limits of agreement based on LME models. The method of computation is the same as Roy's model, but with the covariance estimates set to zero.

In cases where there is negligible covariance between methods, the limits of agree-

ment computed using Roy’s model accord with those computed using Carstensen’s model. In cases where some degree of covariance is present between the two methods, the limits of agreement computed using models will differ. In the presented example, it is shown that Roy’s LoAs are lower than those of Carstensen, when covariance is present.

Importantly, estimates required to calculate the limits of agreement are not extractable, and therefore the calculation must be done by hand.

The presence of the true value term  $\mu_i$  gives rise to an important difference between Carstensen’s and Roy’s models. The fixed effect of Roy’s model comprise of an intercept term and fixed effect terms for both methods, with no reference to the true value of any individual item. In other words, Roy considers the group of items being measured as a sample taken from a population. Therefore a distinction can be made between the two models: Roy’s model is a standard LME model, whereas Carstensen’s model is a more complex additive model.

### 1.3 Introduction to LME Methods for Computing LoAs

Limits of agreement are used extensively for assessing agreement, because they are intuitive and easy to use. Necessarily their prevalence in literature has meant that they are now the best known measurement for agreement, and therefore any newer methodology would benefit by making reference to them.

However, the original Bland-Altman method was developed for two sets of measurements done on one occasion (i.e. independent data), and so this approach is not suitable for replicate measures data. However, as a naive analysis, it may be used to explore the data because of the simplicity of the method.

Bland and Altman (1999) addresses the issue of computing LoAs in the presence of replicate measurements, suggesting several computationally simple approaches. When

repeated measures data are available, it is desirable to use all the data to compare the two methods. Further to Bland and Altman (1986), the computation of the limits of agreement follows from the intermethod bias, and the variance of the difference of measurements. The computation of the inter-method bias is a straightforward subtraction calculation. The variance of differences is easily computable from the variance estimates in the Block -  $\mathbf{\Omega}_i$  matrix, i.e.

$$\text{Var}(y_1 - y_2) = \sqrt{\omega_1^2 + \omega_2^2 - 2\omega_{12}}.$$

Carstensen et al. (2008) demonstrate statistical flaws with two approaches proposed by Bland and Altman (1999) for the purpose of calculating the variance of the inter-method bias when replicate measurements are available. Instead, they recommend a fitted mixed effects model to obtain appropriate estimates for the variance of the inter-method bias. As their interest mainly lies in extending the Bland-Altman methodology, other formal tests are not considered.

## 1.4 Standard Deviation of Differences

In computing limits of agreement, it is first necessary to have an estimate for the standard deviations of the differences. When the agreement of two methods is analyzed using LME models, a clear method of how to compute the standard deviation is required. As the estimate for inter-method bias and the quantile would be the same for both methodologies, the focus hereon is solely on the variance of differences.

The standard deviation of the differences of methods  $x$  and  $y$  is computed using values from the overall VC matrix.

$$\text{Var}(x - y) = \text{Var}(x) + \text{Var}(y) - 2\text{Cov}(x, y)$$

## 1.5 Computation of limits of agreement under Roy's model

The limits of agreement computed by Roy's method are derived from the variance covariance matrix for overall variability. This matrix is the sum of the between subject VC matrix and the within-subject VC matrix. The computation thereof require that the variance of the difference of measurements. This variance is easily computable from the variance estimates in the Block -  $\Omega_i$  matrix, i.e.

$$\text{Var}(y_1 - y_2) = \sqrt{\omega_1^2 + \omega_2^2 - 2\omega_{12}}.$$

The respective estimates computed by both methods are tabulated as follows. Evidently there is close correspondence between both sets of estimates.

## 1.6 Computation of limits of agreement

The computation thereof require that the variance of the difference of measurements. This variance is easily computable from the variance estimates in the Block -  $\Omega_i$  matrix, i.e.

$$\text{Var}(y_1 - y_2) = \sqrt{\omega_1^2 + \omega_2^2 - 2\omega_{12}}.$$

Carstensen et al. (2008) also presents a methodology to compute the limits of agreement based on LME models. The method of computation is similar Roy's model, but for absence of the covariance estimates. In cases where there is negligible covariance between methods, the limits of agreement computed using Roy's model accord with those computed using model described by (1.17). In cases where some degree of covariance is present between the two methods, the limits of agreement computed using models will differ. In the presented example, it is shown that Roy's LOAs are lower than those of (1.17), when covariance between methods is present.

## 1.7 Carstensen's Model

Carstensen et al. (2008) use a LME model for the purpose of comparing two methods of measurement where replicate measurements are available on each item. Their interest lies in generalizing the popular limits-of-agreement (LOA) methodology advocated by Bland and Altman (1986) to take proper cognizance of the replicate measurements.

## 1.8 Carstensen Model

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;

$$y_{mi} = \alpha_m + \mu_i + e_{mi} \quad (e_{mi} \sim N(0, \sigma_m^2)) \quad (1.1)$$

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.

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir} \quad (e_{mi} \sim N(0, \sigma_m^2), c_{mi} \sim N(0, \tau_m^2)) \quad (1.2)$$

Carstensen et al. (2008) proposes a methodology to calculate prediction intervals in the presence of replicate measurements, overcoming problems associated with Bland-Altman methodology in this regard. It is not possible to estimate the interaction variance components  $\tau_1^2$  and  $\tau_2^2$  separately. Therefore it must be assumed that they are equal. The variance of the difference can be estimated as follows:

$$var(y_{1j} - y_{2j}) \quad (1.3)$$



## 1.9 Carstensen's Model (mir model)

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.

Carstensen (2004) proposes linear mixed effects models for deriving conversion calculations similar to Deming's regression, and for estimating variance components for measurements by different methods.

A measurement  $y_{mi}$  by method  $m$  on individual  $i$  is formulated as follows;

$$y_{mi} = \alpha_m + \mu_i + e_{mi} \quad e_{mi} \sim \mathcal{N}(0, \sigma_m^2) \quad (1.4)$$

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.

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir}, \quad e_{mi} \sim \mathcal{N}(0, \sigma_m^2), \quad c_{mi} \sim \mathcal{N}(0, \tau_m^2). \quad (1.5)$$

The following model (in the authors own notation) is formulated as follows, where  $y_{mir}$  is the  $r$ th replicate measurement on subject  $i$  with method  $m$ .

Using Carstensen's notation, a measurement  $y_{mi}$  by method  $m$  on individual  $i$  the measurement  $y_{mir}$  is the  $r$ th replicate measurement on the  $i$ th item by the  $m$ th method, where  $m = 1, 2$ ,  $i = 1, \dots, N$ , and  $r = 1, \dots, n_i$  is formulated as follows;

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + \epsilon_{mir}, \quad e_{mi} \sim \mathcal{N}(0, \sigma_m^2), \quad c_{mi} \sim \mathcal{N}(0, \tau_m^2). \quad (1.6)$$

Here the terms  $\alpha_m$  and  $\mu_i$  represent the fixed effect for method  $m$  and a true value for item  $i$  respectively. The random effect terms comprise an interaction term  $c_{mi}$  and

the residuals  $\epsilon_{mir}$ . The  $c_{mi}$  term represent random effect parameters corresponding to the two methods, having  $E(c_{mi}) = 0$  with  $Var(c_{mi}) = \tau_m^2$ .

The intercept term  $\alpha$  and the  $\beta_m \mu_i$  term follow from Dunn (2002), expressing constant and proportional bias respectively, in the presence of a real value  $\mu_i$ .  $c_{mi}$  is a interaction term to account for replicate, and  $e_{mir}$  is the residual associated with each observation. Since variances are specific to each method, this model can be fitted separately for each method.

Carstensen specifies the variance of the interaction terms as being univariate normally distributed. As such,  $Cov(c_{mi}, c_{m'i}) = 0$ . All the random effects are assumed independent, and that all replicate measurements are assumed to be exchangeable within each method.

Carstensen et al. (2008) uses an approach based on linear mixed effects (LME) models for the purpose of computing the limits of agreement for two methods of measurement, where replicate measurements are taken on items. As the emphasis of this methodology lies on the inter-method bias and the limits of agreement, the two key elements of the Bland-Altman methodology, other formal tests are not described.

With regards to specifying the variance terms, Carstensen remarks that using his approach is common, remarking that *The only slightly non-standard (meaning "not often used") feature is the differing residual variances between methods* (Carstensen, 2010).

In contrast to Roy's model, Carstensen's model requires that commonly used assumptions be applied, specifically that the off-diagonal elements of the between-item and within-item variability matrices are zero. By extension the overall variability off-diagonal elements are also zero. Also, implementation requires that the between-item variances are estimated as the same value:  $g_1^2 = g_2^2 = g^2$ . As a consequence, Carstensen's method does not allow for a formal test of the between-item variability.

$$\begin{pmatrix} \omega_2^1 & 0 \\ 0 & \omega_2^2 \end{pmatrix} = \begin{pmatrix} \tau^2 & 0 \\ 0 & \tau^2 \end{pmatrix} + \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}$$

## 1.10 Carstensen Model

Using Carstensen's notation, a measurement  $y_{mi}$  by method  $m$  on individual  $i$  the measurement  $y_{mir}$  is the  $r$ th replicate measurement on the  $i$ th item by the  $m$ th method, where  $m = 1, 2$ ,  $i = 1, \dots, N$ , and  $r = 1, \dots, n_i$  is formulated as follows;

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + \epsilon_{mir}, \quad e_{mi} \sim \mathcal{N}(0, \sigma_m^2), \quad c_{mi} \sim \mathcal{N}(0, \tau_m^2). \quad (1.7)$$

Of particular importance is terms of the model, a true value for item  $i$  ( $\mu_i$ ). The fixed effect of Roy's model comprise of an intercept term and fixed effect terms for both methods, with no reference to the true value of any individual item. A distinction can be made between the two models: Roy's model is a standard LME model, whereas Carstensen's model is a more complex additive model.

The classical model is based on measurements  $y_{mi}$  by method  $m = 1, 2$  on item  $i = 1, 2, \dots$

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

$$e_{mi} \sim N(0, \sigma_m^2)$$

Here the terms  $\alpha_m$  and  $\mu_i$  represent the fixed effect for method  $m$  and a true value for item  $i$  respectively. The random effect terms comprise an interaction term  $c_{mi}$  and the residuals  $\epsilon_{mir}$ . The  $c_{mi}$  term represent random effect parameters corresponding to the two methods, having  $E(c_{mi}) = 0$  with  $\text{Var}(c_{mi}) = \tau_m^2$ .

The random error term for each response is denoted  $\epsilon_{mir}$  having  $E(\epsilon_{mir}) = 0$ ,  $\text{Var}(\epsilon_{mir}) = \varphi_m^2$ . All the random effects are assumed independent, and that all replicate measurements are assumed to be exchangeable within each method.

When only two methods are to be compared, separate estimates of  $\tau_m^2$  can not be obtained. Instead the average value  $\tau^2$  is obtained and used.

Carstensen's approach is that of a standard two-way mixed effects ANOVA with replicate measurements. With regards to the specification of the variance terms, Carstensen remarks that using his approach is common, remarking that *The only*

*slightly non-standard (meaning "not often used") feature is the differing residual variances between methods* (Carstensen, 2010).

In contrast to Roy's model, Carstensen's model requires that commonly used assumptions be applied, specifically that the off-diagonal elements of the between-item and within-item variability matrices are zero. By extension the overall variability off-diagonal elements are also zero. Also, implementation requires that the between-item variances are estimated as the same value:  $\tau_1^2 = \tau_2^2 = \tau^2$ .

$$\begin{pmatrix} \omega_2^1 & 0 \\ 0 & \omega_2^2 \end{pmatrix} = \begin{pmatrix} \tau^2 & 0 \\ 0 & \tau^2 \end{pmatrix} + \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}$$

The presence of the true value term  $\mu_i$  gives rise to an important difference between Carstensen's and Roy's models. The fixed effect of Roy's model comprise of an intercept term and fixed effect terms for both methods, with no reference to the true value of any individual item. In other words, Roy considers the group of items being measured as a sample taken from a population. Therefore a distinction can be made between the two models: Roy's model is a standard LME model, whereas Carstensen's model is a more complex additive model.

## 1.11 Carstensen's Model

Here the terms  $\alpha_m$  and  $\mu_i$  represent the fixed effect for method  $m$  and a true value for item  $i$  respectively. The random effect terms comprise an interaction term  $c_{mi}$  and the residuals  $\epsilon_{mir}$ . The  $c_{mi}$  term represent random effect parameters corresponding to the two methods, having  $E(c_{mi}) = 0$  with  $\text{Var}(c_{mi}) = \tau_m^2$ . Carstensen specifies the variance of the interaction terms as being univariate normally distributed. As such,  $\text{Cov}(c_{mi}, c_{m'i}) = 0$ . All the random effects are assumed independent, and that all replicate measurements are assumed to be exchangeable within each method.

Even though the separate variances can not be identified, their sum can be estimated by the empirical variance of the differences.

Like wise the separate  $\alpha$  can not be estimated, only their difference can be estimated as  $\bar{D}$

The presence of the true value term  $\mu_i$  gives rise to an important difference between Carstensen's and Roy's models. The fixed effect of Roy's model comprise of an intercept term and fixed effect terms for both methods, with no reference to the true value of any individual item. In other words, Roy considers the group of items being measured as a sample taken from a population. Therefore a distinction can be made between the two models: Roy's model is a standard LME model, whereas Carstensen's model is a more complex additive model.

With regards to specifying the variance terms, Carstensen remarks that using his approach is common, remarking that *The only slightly non-standard (meaning "not often used") feature is the differing residual variances between methods* (Carstensen, 2010).

Carstensen et al. (2008) makes some interesting remarks in this regard.

The only slightly non-standard (meaning "not often used") feature is the differing residual variances between methods.

Further to his model, Carstensen computes the limits of agreement as

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

As the difference between methods is of interest, the item term can be disregarded.

We assume that the variance of the measurements is different for both methods, but it does not mean that the separate variances can be estimated with the data available.

## 1.12 Carstensen's Mixed Models

The above formulation doesn't require the data set to be balanced. However, it does require a sufficient large number of replicates and measurements to overcome the problem of identifiability. The import of which is that more than two methods of measurement may be required to carry out the analysis. There is also the assumptions that observations of measurements by particular methods are exchangeable within subjects. (Exchangeability means that future samples from a population behaves like earlier samples).

Carstensen (2004) uses the above formula to predict observations for a specific individual  $i$  by method  $m$ ;

$$BLUP_{mir} = \hat{\alpha}_m + \hat{\beta}_m \mu_i + c_{mi} \quad (1.8)$$

. Under the assumption that the  $\mu$ s are the true item values, this would be sufficient to estimate parameters. When that assumption doesn't hold, regression techniques (known as updating techniques) can be used additionally to determine the estimates. The assumption of exchangeability can be unrealistic in certain situations. Carstensen (2004) provides an amended formulation which includes an extra interaction term ( $d_{mr} \sim N(0, \omega_m^2)$ ) to account for this.

Carstensen et al. (2008) uses LME models to determine the limits of agreement. Between-subject variation for method  $m$  is given by  $d_m^2$  and within-subject variation is given by  $\lambda_m^2$ . Carstensen et al. (2008) remarks that for two methods  $A$  and  $B$ , separate values of  $d_A^2$  and  $d_B^2$  cannot be estimated, only their average. Hence the assumption that  $d_x = d_y = d$  is necessary. The between-subject variability  $\mathbf{D}$  and within-subject variability  $\mathbf{\Lambda}$  can be presented in matrix form,

$$\mathbf{D} = \begin{pmatrix} d_A^2 & 0 \\ 0 & d_B^2 \end{pmatrix} = \begin{pmatrix} d^2 & 0 \\ 0 & d^2 \end{pmatrix}, \quad \mathbf{\Lambda} = \begin{pmatrix} \lambda_A^2 & 0 \\ 0 & \lambda_B^2 \end{pmatrix}.$$

The variance for method  $m$  is  $d_m^2 + \lambda_m^2$ . Limits of agreement are determined using the standard deviation of the case-wise differences between the sets of measurements

by two methods  $A$  and  $B$ , given by

$$\text{var}(y_A - y_B) = 2d^2 + \lambda_A^2 + \lambda_B^2. \quad (1.9)$$

Importantly the covariance terms in both variability matrices are zero, and no covariance component is present.

Roy (2009b) has demonstrated a methodology whereby  $d_A^2$  and  $d_B^2$  can be estimated separately. Also covariance terms are present in both  $\mathbf{D}$  and  $\mathbf{\Lambda}$ . Using Roy's methodology, the variance of the differences is

$$\text{var}(y_{iA} - y_{iB}) = d_A^2 + \lambda_B^2 + d_A^2 + \lambda_B^2 - 2(d_{AB} + \lambda_{AB}) \quad (1.10)$$

All of these terms are given or determinable in computer output. The limits of agreement can therefore be evaluated using

$$\bar{y}_A - \bar{y}_B \pm 1.96 \times \sqrt{\sigma_A^2 + \sigma_B^2 - 2(\sigma_{AB})}. \quad (1.11)$$

The limits of agreement computed by Roy's method are derived from the variance covariance matrix for overall variability. This matrix is the sum of the between subject VC matrix and the within-subject VC matrix.

The standard deviation of the differences of methods  $x$  and  $y$  is computed using values from the overall VC matrix.

$$\text{var}(x - y) = \text{var}(x) + \text{var}(y) - 2\text{cov}(x, y)$$

The respective estimates computed by both methods are tabulated as follows. Evidently there is close correspondence between both sets of estimates.

The computation thereof require that the variance of the difference of measurements. This variance is easily computable from the variance estimates in the Block -  $\mathbf{\Omega}_i$  matrix, i.e.

$$\text{Var}(y_1 - y_2) = \sqrt{\omega_1^2 + \omega_2^2 - 2\omega_{12}}.$$

Carstensen et al. (2008) also presents a methodology to compute the limits of agreement based on LME models. In many cases the limits of agreement derived from this method accord with those to Roy’s model. However, in other cases dissimilarities emerge. An explanation for this differences can be found by considering how the respective models account for covariance in the observations. Importantly, Carstensen’s underlying model differs from Roy’s model in some key respects, and therefore a prior discussion of Carstensen’s model is required. The method of computation is the same as Roy’s model, but with the covariance estimates set to zero.

Specifying the relevant terms using a bivariate normal distribution, Roy’s model allows for both between-method and within-method covariance. Carstensen et al. (2008) formulate a model whereby random effects have univariate normal distribution, and no allowance is made for correlation between observations.

A consequence of this is that the between-method and within-method covariance are zero. In cases where there is negligible covariance between methods, both sets of limits of agreement are very similar to each other. In cases where there is a substantial level of covariance present between the two methods, the limits of agreement computed using models will differ.

In cases where there is negligible covariance between methods, the limits of agreement computed using Roy’s model accord with those computed using Carstensen’s model. In cases where some degree of covariance is present between the two methods, the limits of agreement computed using models will differ. In the presented example, it is shown that Roy’s LoAs are lower than those of Carstensen, when covariance is present. Importantly, estimates required to calculate the limits of agreement are not extractable, and therefore the calculation must be done by hand. Carstensen presents a model where the variation between items for method  $m$  is captured by  $\sigma_m$  and the within item variation by  $\tau_m$ . Further to his model, Carstensen computes the limits of agreement as

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



Carstensen et al. (2008) presents a data set ‘fat’, which is a comparison of measurements of subcutaneous fat by two observers at the Steno Diabetes Center, Copenhagen. Measurements are in millimeters (mm). Each person is measured three times by each observer. The observations are considered to be ‘true’ replicates.

A linear mixed effects model is formulated, and implementation through several software packages is demonstrated. All of the necessary terms are presented in the computer output. The limits of agreement are therefore,

$$0.0449 \pm 1.96 \times \sqrt{2 \times 0.0596^2 + 0.0772^2 + 0.0724^2} = (-0.220, 0.309). \quad (1.12)$$

? has demonstrated a methodology whereby  $d_A^2$  and  $d_B^2$  can be estimated separately. Also covariance terms are present in both  $\mathbf{D}$  and  $\mathbf{\Lambda}$ . Using Roy’s methodology, the variance of the differences is

$$\text{var}(y_{iA} - y_{iB}) = d_A^2 + \lambda_B^2 + d_B^2 + \lambda_A^2 - 2(d_{AB} + \lambda_{AB}) \quad (1.13)$$

All of these terms are given or determinable in computer output. The limits of agreement can therefore be evaluated using

$$\bar{y}_A - \bar{y}_B \pm 1.96 \times \sqrt{\sigma_A^2 + \sigma_B^2 - 2(\sigma_{AB})}. \quad (1.14)$$

For Carstensen’s ‘fat’ data, the limits of agreement computed using Roy’s method are consistent with the estimates given by Carstensen et al. (2008);  $0.044884 \pm 1.96 \times 0.1373979 = (-0.224, 0.314)$ .

### 1.13 Carstensen’s LOAs

Carstensen presents a model where the variation between items for method  $m$  is captured by  $\sigma_m$  and the within item variation by  $\tau_m$ .

Further to his model, Carstensen computes the limits of agreement as

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

The respective estimates computed by both methods are tabulated as follows. Evidently there is close correspondence between both sets of estimates.

## 1.14 Computing LoAs from LME models

*One important feature of replicate observations is that they should be independent of each other. In essence, this is achieved by ensuring that the observer makes each measurement independent of knowledge of the previous value(s). This may be difficult to achieve in practice.*

## 1.15 Carstensen's Mixed Models

Carstensen (2004) uses the above formula to predict observations for a specific individual  $i$  by method  $m$ ;

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.

Carstensen et al. (2008) proposes a methodology to calculate prediction intervals in the presence of replicate measurements, overcoming problems associated with Bland-Altman methodology in this regard. It is not possible to estimate the interaction variance components  $\tau_1^2$  and  $\tau_2^2$  separately. Therefore it must be assumed that they are equal. The variance of the difference can be estimated as follows:

$$\text{var}(y_{1j} - y_{2j}) \tag{1.15}$$

### 1.15.1 Computation

Modern software packages can be used to fit models accordingly. The best linear unbiased predictor (BLUP) for a specific subject  $i$  measured with method  $m$  has the form  $BLUP_{mir} = \hat{\alpha}_m + \hat{\beta}_m \mu_i + c_{mi}$ , under the assumption that the  $\mu$ s are the true item values.

## 1.16 Other Approaches

? generalize this approach to account for situations where the distributions are not identical, which is commonly the case. The TDI is not consistent and may not preserve its asymptotic nominal level, and that the coverage probability approach of Lin et al. (2002) is overly conservative for moderate sample sizes. This methodology proposed by ? is a regression based approach that models the mean and the variance of differences as functions of observed values of the average of the paired measurements.

Maximum likelihood estimation is used to estimate the parameters. The REML estimation is not considered since it does not lead to a joint distribution of the estimates of fixed effects and random effects parameters, upon which the assessment of agreement is based.

## 1.17 Carstensen 2004 Model

Of particular importance is terms of the model, a true value for item  $i$  ( $\mu_i$ ). The fixed effect of Roy's model comprise of an intercept term and fixed effect terms for both methods, with no reference to the true value of any individual item. A distinction can be made between the two models: Roy's model is a standard LME model, whereas Carstensen's model is a more complex additive model.

Let  $y_{mir}$  denote the  $r$ th replicate measurement on the  $i$ th item by the  $m$ th method, where  $m = 1, 2$ ;  $i = 1, \dots, N$ ; and  $r = 1, \dots, n_i$ . When the design is balanced and there is no ambiguity we can set  $n_i = n$ . The LME model underpinning Roy's approach

can be written

$$y_{mir} = \beta_0 + \beta_m + b_{mi} + \epsilon_{mir}. \quad (1.16)$$

Here  $\beta_0$  and  $\beta_m$  are fixed-effect terms representing, respectively, a model intercept and an overall effect for method  $m$ . The model can be reparameterized by gathering the  $\beta$  terms together into (fixed effect) intercept terms  $\alpha_m = \beta_0 + \beta_m$ . The  $b_{1i}$  and  $b_{2i}$  terms are correlated random effect parameters having  $E(b_{mi}) = 0$  with  $\text{Var}(b_{mi}) = g_m^2$  and  $\text{Cov}(b_{1i}, b_{2i}) = g_{12}$ .

The random error term for each response is denoted  $\epsilon_{mir}$  having  $E(\epsilon_{mir}) = 0$ ,  $\text{Var}(\epsilon_{mir}) = \sigma_m^2$ ,  $\text{Cov}(\epsilon_{1ir}, \epsilon_{2ir}) = \sigma_{12}$ ,  $\text{Cov}(\epsilon_{mir}, \epsilon_{mir'}) = 0$  and  $\text{Cov}(\epsilon_{1ir}, \epsilon_{2ir'}) = 0$ .

Additionally these parameter are assumed to have Gaussian distribution. Two methods of measurement are in complete agreement if the null hypotheses  $H_1: \alpha_1 = \alpha_2$  and  $H_2: \sigma_1^2 = \sigma_2^2$  and  $H_3: g_1^2 = g_2^2$  hold simultaneously. Roy (2009a) uses a Bonferroni correction to control the familywise error rate for tests of  $\{H_1, H_2, H_3\}$  and account for difficulties arising due to multiple testing. Additionally, Roy combines  $H_2$  and  $H_3$  into a single testable hypothesis  $H_4: \omega_1^2 = \omega_2^2$ , where  $\omega_m^2 = \sigma_m^2 + g_m^2$  represent the overall variability of method  $m$ .

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. Their model can be written as

$$y_{mir} = \alpha_m + \mu_i + a_{ir} + c_{mi} + \epsilon_{mir}. \quad (1.17)$$

The fixed effects  $\alpha_m$  and  $\mu_i$  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. The model expressed in (2) describes measurements by  $m$  methods, where  $m = \{1, 2, 3 \dots\}$ . 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  $\tau_m^2$  can not be obtained. To overcome this, the assumption of equality, i.e.  $\tau_1^2 = \tau_2^2$  is required.

There is a substantial difference in the number of fixed parameters used by the respective models; the model in (1.16) requires two fixed effect parameters, i.e. the means of the two methods, for any number of items  $N$ , whereas the model in (1.17) requires  $N + 2$  fixed effects.

Allocating fixed effects to each item  $i$  by (1.17) accords with earlier work on comparing methods of measurement, such as Grubbs (1948). However allocation of fixed effects in ANOVA models suggests that the group of items is itself of particular interest, rather than as a representative sample used of the overall population. However this approach seems contrary to the purpose of LOAs as a prediction interval for a population of items. Conversely, Roy (2009a) uses a more intuitive approach, treating the observations as a random sample population, and allocating random effects accordingly.

## 1.18 Bendix Carstensen's data sets

Carstensen et al. (2008) formulates an LME model, both in the absence and the presence of an interaction term. ? uses both to demonstrate the importance of using an interaction term. Failure to take the replication structure into account results in over-estimation of the limits of agreement. For the Carstensen estimates below, an interaction term was included when computed.

Carstensen et al. (2008) describes the sampling method when discussing of a motivating example. Diabetes patients attending an outpatient clinic in Denmark have their  $HbA_{1c}$  levels routinely measured at every visit. Venous and Capillary blood samples were obtained from all patients appearing at the clinic over two days.

Samples were measured on four consecutive days on each machines, hence there are five analysis days. Carstensen notes that every machine was calibrated every day to the manufacturers guidelines.

### 1.18.1 Limits of agreement for Carstensen's data

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

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

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

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

### 1.18.2 Using LME models to create Prediction Intervals

#### Carstensen et al - Mixed Models

Carstensen et al [4] 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;

$$y_{mi} = \alpha_m + \mu_i + e_{mi} \quad (e_{mi} \sim N(0, \sigma_m^2)) \quad (1.18)$$

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.

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir} \quad (e_{mi} \sim N(0, \sigma_m^2), c_{mi} \sim N(0, \tau_m^2)) \quad (1.19)$$

Carstensen *et al* 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;

$$y_{mi} = \alpha_m + \mu_i + e_{mi} \quad (e_{mi} \sim N(0, \sigma_m^2)) \quad (1.20)$$

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.

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir} \quad (1.21)$$

The following model (in the authors own notation) is formulated as follows, where  $y_{mir}$  is the  $r$ th replicate measurement on subject  $i$  with method  $m$ .

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

$$y_{mir} = \alpha_m + \beta_m \mu_i + c_{mi} + e_{mir} \quad (1.23)$$

$$e_{mi} \sim N(0, \sigma_m^2), c_{mi} \sim N(0, \tau_m^2)$$

The intercept term  $\alpha$  and the  $\beta_m \mu_i$  term follow from *Dunn Dunn* (2002), expressing constant and proportional bias respectively, in the presence of a real value  $\mu_i$ .  $c_{mi}$  is a interaction term to account for replicate, and  $e_{mir}$  is the residual associated with each observation. Since variances are specific to each method, this model can be fitted separately for each method. The above formulation doesn't require the data set to be balanced. However, it does require a sufficient large number of replicates and measurements to overcome the problem of identifiability. The import of which is that more than two methods of measurement may be required to carry out the analysis.

There is also the assumptions that observations of measurements by particular methods are exchangeable within subjects. ***Exchangeability*** means that future samples from a population behaves like earlier samples).

*One important feature of replicate observations is that they should be independent of each other. In essence, this is achieved by ensuring that the observer makes each measurement independent of knowledge of the previous value(s). This may be difficult to achieve in practice.*

## Using LME models to create Prediction Intervals

Carstensen et al. (2008) proposes a methodology to calculate prediction intervals in the presence of replicate measurements, overcoming problems associated with Bland-Altman methodology in this regard. It is not possible to estimate the interaction variance components  $\tau_1^2$  and  $\tau_2^2$  separately. Therefore it must be assumed that they are equal. The variance of the difference can be estimated as follows:

$$var(y_{1j} - y_{2j}) \tag{1.24}$$



### 1.18.3 Carstensen's Mixed Models

Carstensen *et al*[4] proposes linear mixed effects models for deriving conversion calculations similar to Deming's regression, and for estimating variance components for measurements by different methods. The following model ( in the authors own notation) is formulated as follows, where  $y_{mir}$  is the  $r$ th replicate measurement on subject  $i$  with method  $m$ .

$$y_{mir} = \alpha_m + \beta_m \mu_i + c_{mi} + e_{mir} \quad (e_{mi} \sim N(0, \sigma_m^2), c_{mi} \sim N(0, \tau_m^2)) \quad (1.25)$$

The intercept term  $\alpha$  and the  $\beta_m \mu_i$  term follow from Dunn[7], expressing constant and proportional bias respectively , in the presence of a real value  $\mu_i$ .  $c_{mi}$  is a interaction term to account for replicate, and  $e_{mir}$  is the residual associated with each observation. Since variances are specific to each method, this model can be fitted separately for each method.

This model includes a method by item interaction term.

Carstensen presents two models. One for the case where the replicates, and a second for when they are linked.

Carstensen's model does not take into account either between-item or within-item covariance between methods.

In the presented example, it is shown that Roy's LoAs are lower than those of Carstensen.

$$\begin{pmatrix} \omega_2^1 & 0 \\ 0 & \omega_2^2 \end{pmatrix} = \begin{pmatrix} \tau^2 & 0 \\ 0 & \tau^2 \end{pmatrix} + \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}$$

Carstensen *et al*[4] 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.

$$y_{mi} = \alpha_m + \mu_i + e_{mi} \quad e_{mi} \sim \mathcal{N}(0, \sigma_m^2) \quad (1.26)$$

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.

#### 1.18.4 Computing LOAs from LME models

*One important feature of replicate observations is that they should be independent of each other. In essence, this is achieved by ensuring that the observer makes each measurement independent of knowledge of the previous value(s). This may be difficult to achieve in practice.*

#### 1.18.5 Carstensen's LOAs

Carstensen presents a model where the variation between items for method  $m$  is captured by  $\sigma_m$  and the within item variation by  $\tau_m$ .

Further to his model, Carstensen computes the limits of agreement as

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

The respective estimates computed by both methods are tabulated as follows. Evidently there is close correspondence between both sets of estimates.

Bxc2008 formulates an LME model, both in the absence and the presence of an interaction term. BXC2008 uses both to demonstrate the importance of using an interaction term. Failure to take the replication structure into account results in over-estimation of the limits of agreement. For the Carstensen estimates below, an interaction term was included when computed.

### 1.18.6 Bendix Carstensen's data sets

Carstensen et al. (2008) describes the sampling method when discussing of a motivating example. Diabetes patients attending an outpatient clinic in Denmark have their  $HbA_{1c}$  levels routinely measured at every visit. Venous and Capillary blood samples were obtained from all patients appearing at the clinic over two days.

Samples were measured on four consecutive days on each machines, hence there are five analysis days. Carstensen notes that every machine was calibrated every day to the manufacturers guidelines.

## 1.19 Correlation terms

The methodology proposed by Roy (2009b) is largely based on Hamlett et al. (2004), which in turn follows on from Lam et al. (1999).

Hamlett re-analyses the data of Lam et al. (1999) to generalize their model to cover other settings not covered by the Lam method.

In many cases, repeated observation are collected from each subject in sequence and/or longitudinally.

$$y_i = \alpha + \mu_i + \epsilon$$

Hamlett et al. (2004) demonstrated how the between-subject and within subject variabilities can be expressed in terms of correlation terms.

$$\mathbf{D} = \begin{pmatrix} \sigma_A^2 \rho_A & \sigma_A \sigma_B \rho_{AB} \delta \\ \sigma_A \sigma_B \rho_{AB} \delta & \sigma_B^2 \rho_B \end{pmatrix}$$

$$\mathbf{\Lambda} = \begin{pmatrix} \sigma_A^2 (1 - \rho_A) & \sigma_{AB} (1 - \delta) \\ \sigma_{AB} (1 - \delta) & \sigma_B^2 (1 - \rho_B) \end{pmatrix}.$$

$\rho_A$  describe the correlations of measurements made by the method  $A$  at different times. Similarly  $\rho_B$  describe the correlation of measurements made by the method  $B$

at different times. Correlations among repeated measures within the same method are known as intra-class correlation coefficients.  $\rho_{AB}$  describes the correlation of measurements taken at the same same time by both methods. The coefficient  $\delta$  is added for when the measurements are taken at different times, and is a constant of less than 1 for linked replicates. This is based on the assumption that linked replicates measurements taken at the same time would have greater correlation than those taken at different times. For unlinked replicates  $\delta$  is simply 1. Hamlett et al. (2004) provides a useful graphical depiction of the role of each correlation coefficients.

Bivariate correlation coefficients have been shown to be of limited use in method comparison studies (Bland and Altman, 1986). However, recently correlation analysis has been developed to cope with repeated measurements, enhancing their potential usefulness. Roy incorporates the use of correlation into his methodology.

In addition to the variability tests, Roy advises that it is preferable that a correlation of greater than 0.82 exist for two methods to be considered interchangeable. However if two methods fulfil all the other conditions for agreement, failure to comply with this one can be overlooked. Indeed Roy demonstrates that placing undue importance to it can lead to incorrect conclusions. Roy (2009b) remarks that current computer implementations only gives overall correlation coefficients, but not their variances. Consequently it is not possible to carry out inferences based on all overall correlation coefficients.

## 1.20 Variance Ratios

The approach proposed by Roy deals with the question of agreement, and indeed interchangeability, as developed by Bland and Altman's corpus of work. In the view of Dunn, a question relevant to many practitioners is which of the two methods is more precise.

The relationship between precision and the within-item and between-item variability must be established. Roy establishes the equivalence of repeatability and within-

item variability, and hence precision. The method with the smaller within-item variability can be deemed to be the more precise.

A useful approach is to compute the confidence intervals for the ratio of within-item standard deviations (equivalent to the ratio of repeatability coefficients), which can be interpreted in the usual manner.

In fact, the ratio of within-item standard deviations, with the attendant confidence interval, can be determined using a single R command: `intervals()`.

Pinheiro and Bates (pg 93-95) give a description of how confidence intervals for the variance components are computed. Furthermore a complete set of confidence intervals can be computed to complement the variance component estimates.

What is required is the computation of the variance ratios of within-item and between-item standard deviations.

A naive approach would be to compute the variance ratios by relevant F distribution quantiles. However, the question arises as to the appropriate degrees of freedom. Limits of agreement are easily computable using the LME framework. While we will not be considering this analysis, a demonstration will be provided in the example.

## **1.21 BXC2008 presents - Carstensen's Limits of agreement**

In cases where there is negligible covariance between methods, the limits of agreement computed using Roy's model accord with those computed using Carstensen's model. In cases where some degree of covariance is present between the two methods, the limits of agreement computed using models will differ. In the presented example, it is shown that Roy's LoAs are lower than those of Carstensen, when covariance is present.

Importantly, estimates required to calculate the limits of agreement are not extractable, and therefore the calculation must be done by hand.

## 1.22 Interaction Terms in Model

Further to Barnhart et al. (2007), if the measurements by a method on an item are not necessarily true replications, e.g., repeated measures over time, then additional terms may be needed for  $e_{mir}$ . ? also addresses this issue by the addition of an interaction term (i.e. a random effect)  $u_{mi}$ , yielding

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

The additional interaction term is characterized as  $u_{mi} \sim \mathcal{N}(0, \tau_m^2)$  (?).

This extra interaction term provides a source of extra variability, but this variance is not relevant to computing the case-wise differences.

? advises that the formulation of the model should take the exchangeability (in other words, whether or not the measurements are ‘true replicates’) into account. If there is a linkage between measurements (therefore not ‘true’ replicates), the ‘item by replicate’ should be included in the model. If there is no linkage, and the replicates are indeed true replicates, the interaction term should be omitted.

? demonstrates how to compute the limits of agreement for two methods in the case of linked measurements. As a surplus source of variability is excluded from the computation, the limits of agreement are not unduly wide, which would have been the case if the measurements were treated as true replicates.

? also assigns a random effect  $u_{mi}$  for each response  $y_{mir}$ . Importantly Roy’s model assumes linkage.

Carstensen et al. (2008) formulates an LME model, both in the absence and the presence of an interaction term. ? uses both to demonstrate the importance of using an interaction term. Failure to take the replication structure into account results in over-estimation of the limits of agreement. For the Carstensen estimates below, an interaction term was included when computed.

Carstensen presents a model where the variation between items for method  $m$  is captured by  $\sigma_m$  and the within item variation by  $\tau_m$ .

Further to his model, Carstensen computes the limits of agreement as

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

## 1.23 Difference Between Approaches

Carstensen presents two models. One for the case where the replicates, and a second for when they are linked.

Carstensen's model does not take into account either between-item or within-item covariance between methods.

In the presented example, it is shown that Roy's LoAs are lower than those of Carstensen.

$$\begin{pmatrix} \omega_2^1 & 0 \\ 0 & \omega_2^2 \end{pmatrix} = \begin{pmatrix} \tau^2 & 0 \\ 0 & \tau^2 \end{pmatrix} + \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}$$

## 1.24 Differences Between Models

Carstensen et al. (2008) also presents a methodology to compute the limits of agreement based on LME models. In many cases the limits of agreement derived from this method accord with those to Roy's model. However, in other cases dissimilarities emerge. An explanation for this differences can be found by considering how the respective models account for covariance in the observations. Specifying the relevant terms using a bivariate normal distribution, Roy's model allows for both between-method and within-method covariance. Carstensen et al. (2008) formulate a model whereby random effects have univariate normal distribution, and no allowance is made for correlation between observations.

A consequence of this is that the between-method and within-method covariance are zero. In cases where there is negligible covariance between methods, both sets of limits of agreement are very similar to each other. In cases where there is a substantial level of covariance present between the two methods, the limits of agreement computed using models will differ.

There is a substantial difference in the number of fixed parameters used by the respective models. For the model in (1.16) requires two fixed effect parameters, i.e. the means of the two methods, for any number of items  $N$ . In contrast, the model described by (1.17) requires  $N + 2$  fixed effects for  $N$  items. The inclusion of fixed effects to account for the 'true value' of each item greatly increases the level of model complexity.

When only two methods are compared, Carstensen et al. (2008) notes that separate estimates of  $\tau_m^2$  can not be obtained due to the model over-specification. To overcome this, the assumption of equality, i.e.  $\tau_1^2 = \tau_2^2$ , is required.

## 1.25 Differences

Roy (2009b) has demonstrated a methodology whereby  $d_A^2$  and  $d_B^2$  can be estimated



separately. Also covariance terms are present in both  $\mathbf{D}$  and  $\mathbf{\Lambda}$ . Using Roy's methodology, the variance of the differences is

$$\text{var}(y_{iA} - y_{iB}) = d_A^2 + \lambda_B^2 + d_B^2 + \lambda_A^2 - 2(d_{AB} + \lambda_{AB}) \quad (1.27)$$

All of these terms are given or determinable in computer output. The limits of agreement can therefore be evaluated using

$$\bar{y}_A - \bar{y}_B \pm 1.96 \times \sqrt{\sigma_A^2 + \sigma_B^2 - 2(\sigma_{AB})}. \quad (1.28)$$

In cases where there is negligible covariance between methods, the limits of agreement computed using Roy's model accord with those computed using Carstensen's model. In cases where some degree of covariance is present between the two methods, the limits of agreement computed using models will differ. In the presented example, it is shown that Roy's LoAs are lower than those of Carstensen, when covariance is present.

Importantly, estimates required to calculate the limits of agreement are not extractable, and therefore the calculation must be done by hand. Carstensen presents a model where the variation between items for method  $m$  is captured by  $\sigma_m$  and the within item variation by  $\tau_m$ .

In contrast to Roy's model, Carstensen's model requires that commonly used assumptions be applied, specifically that the off-diagonal elements of the between-item and within-item variability matrices are zero. By extension the overall variability off-diagonal elements are also zero. Also, implementation requires that the between-item variances are estimated as the same value:  $g_1^2 = g_2^2 = g^2$ .

## 1.26 Repeated Measurements

In cases where there are repeated measurements by each of the two methods on the same subjects, Bland Altman suggest calculating the mean for each method on each subject and use these pairs of means to compare the two methods. The estimate of bias

will be unaffected using this approach, but the estimate of the standard deviation of the differences will be too small, because of the reduction of the effect of repeated measurement error. Bland Altman propose a correction for this. Carstensen attends to this issue also, adding that another approach would be to treat each repeated measurement separately.

## 1.27 LME

Consistent with the conventions of mixed models, ? formulates the measurement  $y_{ij}$  from method  $i$  on individual  $j$  as follows;

$$y_{ij} = P_{ij}\theta + W_{ij}v_i + X_{ij}b_j + Z_{ij}u_j + \epsilon_{ij}, (j = 1, 2, i = 1, 2, \dots, n) \quad (1.29)$$

The design matrix  $P_{ij}$ , with its associated column vector  $\theta$ , specifies the fixed effects common to both methods. The fixed effect specific to the  $j$ th method is articulated by the design matrix  $W_{ij}$  and its column vector  $v_i$ . The random effects common to both methods is specified in the design matrix  $X_{ij}$ , with vector  $b_j$  whereas the random effects specific to the  $i$ th subject by the  $j$ th method is expressed by  $Z_{ij}$ , and vector  $u_j$ . Noticeably this notation is not consistent with that described previously. The design matrices are specified so as to includes a fixed intercept for each method, and a random intercept for each individual. Additional assumptions must also be specified;

$$v_{ij} \sim N(0, \Sigma), \quad (1.30)$$

These vectors are assumed to be independent for different  $i$ s, and are also mutually independent. All Covariance matrices are positive definite. In the above model effects can be classed as those common to both methods, and those that vary with method. When considering differences, the effects common to both effectively cancel each other out. The differences of each pair of measurements can be specified as following;

$$d_{ij} = X_{ij}b_j + Z_{ij}u_j + \epsilon_{ij}, (j = 1, 2, i = 1, 2, \dots, n) \quad (1.31)$$

This formulation has separate distributional assumption from the model stated previously.

This agreement covariate  $x$  is the key step in how this methodology assesses agreement.

## 1.28 Difference Variance further to Carstensen

Carstensen et al. (2008) states a model where the variation between items for method  $m$  is captured by  $\tau_m$  (our notation  $d_m^2$ ) and the within-item variation by  $\sigma_m$ .

*The formulation of this model is general and refers to comparison of any number of methods however, if only two methods are compared, separate values of  $\tau_1^2$  and  $\tau_2^2$  cannot be estimated, only their average value  $\tau$ , so in the case of only two methods we are forced to assume that  $\tau_1 = \tau_2 = \tau$  (Carstensen et al., 2008).*

Another important point is that there is no covariance terms, so further to Carstensen et al. (2008) the variance covariance matrices for between-item and within-item variability are respectively.

$$\mathbf{D} = \begin{pmatrix} d_2^1 & 0 \\ 0 & d_2^2 \end{pmatrix}$$

and  $\mathbf{\Sigma}$  is constructed as follows:

$$\mathbf{\Sigma} = \begin{pmatrix} \sigma_2^1 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}$$

Under this model the limits of agreement should be computed based on the standard deviation of the difference between a pair of measurements by the two methods on a new individual,  $j$ , say:

$$\text{var}(y_{1j} - y_{2j}) = 2d^2 + \sigma_1^2 + \sigma_2^2$$

Further to his model, Carstensen computes the limits of agreement as

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

## 1.29 Relevance of Roy's Methodology

The relevance of Roy's methodology is that estimates for the between-item variances for both methods  $\hat{d}_m^2$  are computed. Also the VC matrices are constructed with covariance terms and, so the difference variance must be formulated accordingly.

$$\hat{\alpha}_1 - \hat{\alpha}_2 \pm \sqrt{\hat{d}_1^2 + \hat{d}_1^2 + \hat{\sigma}_1^2 + \hat{\sigma}_2^2 - 2\hat{d}_{12} - 2\hat{\sigma}_1\hat{\sigma}_2}$$

Roy (2009b) considers the problem of assessing the agreement between two methods with replicate observations in a doubly multivariate set-up using linear mixed effects models.

Roy (2009b) uses examples from Bland and Altman (1986) to be able to compare both types of analysis.

Roy (2009b) proposes a LME based approach with Kronecker product covariance structure with doubly multivariate setup to assess the agreement between two methods. This method is designed such that the data may be unbalanced and with unequal numbers of replications for each subject.

The maximum likelihood estimate of the between-subject variance covariance matrix of two methods is given as  $D$ . The estimate for the within-subject variance covariance matrix is  $\hat{\Sigma}$ . The estimated overall variance covariance matrix 'Block  $\Omega_i$ ' is the addition of  $\hat{D}$  and  $\hat{\Sigma}$ .

$$\text{Block } \Omega_i = \hat{D} + \hat{\Sigma} \tag{1.32}$$

### 1.30 Extension of Roy's methodology

Roy's methodology is constructed to compare two methods in the presence of replicate measurements. Necessarily it is worth examining whether this methodology can be adapted for different circumstances.

An implementation of Roy's methodology, whereby three or more methods are used, is not feasible due to computational restrictions. Specifically there is a failure to reach convergence before the iteration limit is reached. This may be due to the presence of additional variables, causing the problem of non-identifiability. In the case of two variables, it is required to estimate two variance terms and four correlation terms, six in all. For the case of three variabilities, three variance terms must be estimated as well as nine correlation terms, twelve in all. In general for  $n$  methods has  $2 \times T_n$  variance terms, where  $T_n$  is the triangular number for  $n$ , i.e. the addition analogue of the factorial. Hence the computational complexity quite increases substantially for every increase in  $n$ .

Should an implementation be feasible, further difficulty arises when interpreting the results. The fundamental question is whether two methods have close agreement so as to be interchangeable. When three methods are present in the model, the null hypothesis is that all three methods have the same variability relevant to the respective tests. The outcome of the analysis will either be that all three are interchangeable or that all three are not interchangeable.

The tests would not be informative as to whether any two of those three were interchangeable, or equivalently if one method in particular disagreed with the other two. Indeed it is easier to perform three pair-wise comparisons separately and then to combine the results.

### 1.31 Roy's methodology for single measurements

Roy's methodology follows from the decomposition for the covariance matrix of the response vector  $y_i$ , as presented in Hamlett et al. (2004). The decomposition depends on the estimation of correlation terms, which would be absent in the single measurement case. Indeed there can be no within-subject variability if there are no repeated terms for it to describe. There would only be the covariance matrix of the measurements by both methods, which doesn't require the use of LME models. To conclude, simple existing methodologies would be the correct approach where there only one measurements by each method. Roy's methodology is not suitable for the case of single measurements because it follows from the decomposition for the covariance matrix of the response vector  $y_i$ , as presented in Hamlett et al. (2004). The decomposition depends on the estimation of correlation terms, which would be absent in the single measurement case. Indeed there can be no within-subject variability if there are no repeated terms for it to describe. There would only be the covariance matrix of the measurements by both methods, which doesn't require the use of LME models. To conclude, simpler existing methodologies, such as Deming regression, would be the correct approach where there only one measurements by each method.

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## 1.32 Assumptions on Variability

Aside from the fixed effects, another important difference is that Carstensen's model requires that particular assumptions be applied, specifically that the off-diagonal elements of the between-item and within-item variability matrices are zero. By extension the overall variability off diagonal elements are also zero.

Also, implementation requires that the between-item variances are estimated as the same value:  $g_1^2 = g_2^2 = g^2$ . Necessarily Carstensen's method does not allow for a formal test of the between-item variability.

$$\begin{pmatrix} \omega_2^1 & 0 \\ 0 & \omega_2^2 \end{pmatrix} = \begin{pmatrix} g^2 & 0 \\ 0 & g^2 \end{pmatrix} + \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}$$

In cases where the off-diagonal terms in the overall variability matrix are close to zero, the limits of agreement due to ? are very similar to the limits of agreement that follow from the general model.

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