Chapter 1

Bradley Blackwood

1.1 Bartko's Bradley-Blackwood Test

This is a regression based approach that performs a simultaneous test for the equivalence of means and variances of the respective methods.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.

$$D = (X_1 - X_2) \tag{1.1}$$

$$M = (X_1 + X_2)/2 \tag{1.2}$$

The Bradley Blackwood Procedure fits D on M as follows:

$$D = \beta_0 + \beta_1 M \tag{1.3}$$

- 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.
- 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.

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

Bartko's Discussion of BB

Let $y = X_1 - X_2$ and $x = (X_1 - X_2)/2$. The Bradley-Blackwood procedure fits y on x, such that

$$y = \beta_0 + \beta_1 x$$

The slope and intercepte are given bu

$$beta_1 = \frac{(\sigma_1^2 = \sigma_2^2)}{2\sigma_x^2}$$

1.2 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.

1.3 Conclusions about Existing Methodologies

The Bland Altman methodology is well noted for its ease of use, and can be easily implemented with most software packages. Also it doesn't 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 these 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.

There is no formal testing procedure provided. Rather, it is upon the practitioner opinion to judge the outcome of the methodology.

Bartko's Ellipse

$$\frac{x-\bar{x}}{\sigma_x^2} - \frac{2\rho(x-\bar{x})(y-\bar{y})}{\sigma_x\sigma_y} + \frac{y-\bar{y}}{\sigma_y^2} = \chi^2(2df_(1-\rho^2)$$

1.4 A regression based approach based on Bland Altman Analysis

Bland and Altman have stated that regression analysis offers insights into method comparison studies. Regression methods can determine the presence of bias, and the levels of constant bias and proportional bias thereof Ludbrook (1997, 2002). While they are informative about inter-method bias, Regression methods offer the analyst no insights into the relative precision of both methods. These methods can be employed in conversion problems, however errors are attended. ***Lu et al*** used such a technique in their comparison of DXA scanners. They also used the Blackwood Bradley test. However it was shown that, for particular comparisons, agreement between methods was indicated according to one test, but lack of agreement was indicated by the other.

Remarks

- Pearson's Correlation of (x,y) is the same as Pitman's correlation of sums and differences.
- Techniques for plotting an ellipse can be found in Douglas Altman's book.

1.5 The MCR R pacakge - Regression Techniques for MCS

The ***mcr*** packages provides a set of regression techniques to quantify the relation between two measurement methods.

In particular, it address regression problems with errors in both variables, but without repeated measurements. The ***mcr*** package follows the CLSI EP09-A3 recommendations for analytical method comparison and estimation of bias using patient samples.

Methods featured in the ***mcr*** *package*

- Deming Regression
- Weighted Deming Regression

- Passing-Bablock Regression

The *creatinine* gives the blood and serum preoperative creatinine measurements in 110 heart surgery patients.

```
library("mcr")
data("creatinine", package="mcr")
tail(creatinine)



fit.lr <- mcreg(as.matrix(creatinine), method.reg="LinReg", na.rm=TRUE)
fit.wlr <- mcreg(as.matrix(creatinine), method.reg="WLinReg", na.rm=TRUE)
compareFit( fit.lr, fit.wlr )
```

1.6 KP

Most residual covariance structures are design for one within-subject factor. However two or more may be present. For such cases, an approppriate approach would be the residual covariance structure using Kronecker product of the underlying within-subject factor specific covariances structure.

Chapter 2

REGRESSION

2.1 Simple Linear Regression

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

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

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.

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 covariates of the plot accord closely with the $X = Y$ line.

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.

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).

2.2 Constant and Proportional Bias

Linear Regression is a commonly used technique for comparing paired assays. The Intercept and Slope can provide estimates for the constant bias and proportional bias occurring between both methods. 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.

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.

Pitman's Test on Correlated variances

$H_0 \, : \, \sigma_1^2 = \sigma_2^2$

$H_0 \, : \, \sigma_1^2 = \sigma_2^2$

Pitman's test is identical to the slope equal to zero in the regression of y on x.

2.3 Regression Approaches to MCS

- This section of the paper will discuss several regression-based techniques for method comparison study, such as *Deming Regression*. - This section will highlight several useful characteristics of the data that regression based techniques may highlight, and also the limitations of these techniques.

Deming Regression

Whereas the OLS method assumes that only the Y measurements are associated with random measurement errors, the Deming method takes measurement errors for both methods of measurement into account.

The presence of bias may impair agreement between the two analytical methods.

types of bias

- constant bais
- proportionl bias

2.4 Passing and bablok

proposed an linear regression procedure with no special assumptions regarding the distribution of the data. This non parametric method is based on ranking the observatons so it is computationally intensive. The result is independent of the assignment of the reference method (X) and the reference method (Y).

2.4.1 Passing and Bablok (1983)

Passing & Bablok have described a linear regression model that are without the usual assumptions regarding the distribution of the samples and the measurement errors. The result does not depend on the assignment of the methods (or instruments) to X and Y. The slope and intercept are calculated with their 95% confidence interval.Hypothesis tests on the slope and intercept maybe then carried out.

If the hypothesis of the intercept is rejected, then it is concluded that it is significant different from 0 and both raters differ at least by a constant amount.
If the hypothesis of the slope is rejected, then it is concluded that the slope is significant different from 1 and there is at least a proportional difference between the two raters.

2.4.2 Passing-Bablok Regression

Passing & Bablok (1983) have described a linear regression procedure with no special assumptions regarding the distribution of the samples and the measurement errors. The result does not depend on the assignment of the methods (or instruments) to X and Y. The slope B and intercept A are calculated with their 95% confidence interval. These confidence intervals are used to determine whether there is only a chance difference between B and 1 and between A and 0.

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" a new biometric method procedure for testing the equality of measurements from two different analytical methods" J Clin. Chem Clin.BioChem. [21], 709-720 (1983)

2.4.5 Implementation with `R`

```
library(mcr)
```

The presence of bias may impair agreement between the two analytical methods.

types of bias

- constant bais
- proportionl bias

Bibliography

Altman, D. and J. Bland (1983). Measurement in medicine: The analysis of method comparison studies. *Journal of the Royal Statistical Society. Series D (The Statistician) 32*(3), 307–317.

Bland, J. and D. Altman (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *The Lancet i*, 307–310.

Cornbleet, P. J. and D. Cochrane (1979). Regression methods for assessing agreement between two methods of clinical measurement. *Journal of Clinical Chemistry 24*(2), 342–345.

Ludbrook, J. (1997). Comparing methods of measurement. *Clinical and Experimental Pharmacology and Physiology 24*, 193–203.

Ludbrook, J. (2002). Statistical techniques for comparing measurers and methods of measurement: a critcal review. *Clinical and Experimental Pharmacology and Physiology 29*, 527–536.