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Chapter 1

Errors-in-variables Regression

1.1 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 co-variates 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).

1.2 Errors-in-variables models

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

1.3 Deming Regression

1.3.1 Introduction

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

1.3.2 Origin of Deming Regression

Kummel (1879)

Deming regression is a type of error-in-variable regression approach that assumes that the ratio $\lambda = \sigma^2_{epsilon}/\sigma^2_{\eta}$ is known. This approach would be appropriate when errors in y and x are both caused by measurements, and the accuracy of measuring devices or procedures are known. The case when $\lambda = 1$ is also known as the ***orthogonal regression***.

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

1.3.3 Comparison to SLR

Deming regression is a regression fitting approach that assumes error in both variables. The sum of squared distances from measured sets of values to the regression line is minimized at an angles specified by the ratio λ of the residual variance of both variables.

The variance of the ratio,λ, specifies the angle. When λ is one, the angle is 45 degrees. In ordinary linear regression, the distances are minimized in the vertical directions (Linnet, 1999).

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

1.3.4 Deming Regression for MCS

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

1.3.5 Implementations

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

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

1.3.6 Drawbacks of Deming Regression

Deming's Regression suffers from some crucial drawback. Firstly it is computationally complex, and it requires specific software packages to perform calculations. Secondly it is uninformative about the comparative precision of two methods of measurement. Most importantly Carroll and Ruppert (1996) states that

Deming's regression is acceptable only when the precision ratio (λ, in their paper as η) is correctly specified, but in practice this is often not the case, with the λ being underestimated. This underestimation leads to an overcorrection for attenuation.

1.3.7 Diagnostics

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.

1.3.8 Single measurements

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

1.3.9 Performance in the presence of outliers

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

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

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

1.3.10 Weighted Deming Regression

Weighted Linear Regression

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

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

1.3.11 Deming Regression : Parameters and Estimation

RMSE

The root mean squared error is an estimate of the total error of the slope and includes the random error and the systemic error.

Estimating the Variance ratio

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

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

$$x_i = \mu + \epsilon_{xi}$$

$$y_i = \mu + \beta_1 + \epsilon_{yi}$$

The residuals can be expressed as

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

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

$$\lambda = \frac{\sigma^2_{yx}}{\sigma^2_y}. \tag{1.1}$$

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

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

1.3.12 Using LME models to estimate the ratio (BXC)

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

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

1.3.13 Estimating the variance ratio (Linnet)

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

1.4 Other Regression Approaches

1.4.1 Model I and II Regression

Model I regression is unsuitable for method comparison studies. Even in the case where one method is a gold standard , it is disputed as to whether it is a valid approach. Model II regression is suitable for method comparison studies, but it is more difficult to execute. Both Model I and II regression models are unduly influenced by outliers. Regression Models can not easily be used to analyze repeated measurements

1.4.2 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.

1.4.3 Cornbleet - Cochran

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

- Model II regression [Test V Test] In this type of analysis,both of the measurement methods are test methods, with both expected to be subject to error. Deming regression is an approach to model II regression.
- Model I regression [Criterion v Test] [Cornbleet Gochman 1979] define this analysis as the case in which the independent variable, X, is measured without error, with y as the dependent variable.
- In method comparison studies, the X variable is a precisely measured reference method. In the [Cornbleet Gochman 1979] paper It is argued that criterion may be regarded as the correct value. Other papers dispute this.

1.5 Advanced Regression Methods

In this section we examine some of the more advanced regression based approach employed in method comparison studies.

1.5.1 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.

1.5.2 Bivariate Least Squares Regression

Since there are errors in both methods, a regression technique that takes into account the individual errors in both axes (bivariate least-squares, BLS) should be used. In this paper, we demonstrate that the errors made in estimating the regression coefficients by the BLS method are fewer than with the ordinary least-squares (OLS) or weighted least-squares (WLS) regression techniques and that the coefficient can be considered normally distributed.

1.5.3 Least Products Regression

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

- Model II regression analysis caters for cases in which random error is attached to both dependent and independent variables. Comparing methods of measurement is just such a case.(Ludbrook)
- Least products regression is the reviewer's preferred technique for analysing the Model II case. In this, the sum of the products of the vertical and horizontal deviations of the x,y values from the line is minimized.
- Least products regression analysis is suitable for calibrating one method against another. It is also a sensitive technique for detecting and distinguishing fixed and proportional bias between methods.

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

1.6 Regression Based Approaches

1.6.1 Comparison of Model II regressions

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

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

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.

Carroll, R. and D. Ruppert (1996). The use and misuse of orthogonal regression in linear errors-in-variables models. *The American Statistician 50*(1), 1–6.

Carstensen, B., J. Simpson, and L. C. Gurrin (2008). Statistical models for assessing agreement in method comparison studies with replicate measurements. *The International Journal of Biostatistics 4*(1).

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.

Kummel, C. (1879). Reduction of observation equations which contain more than one observed quantity. *The Analyst 6*, 97–105.

Linnet, K. (1999). Necessary sample size for method comparison studies based on regression analysis. *Clinical Chemistry 45*(6), 882–894.

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.

Pinheiro, J. and D. Bates (1994). *Mixed Effects Models in S and S plus* (2nd ed.). Reading, Massachusetts: Springer.