0.1 Regression Methods

Conventional regression models are estimated using the ordinary least squares (OLS) technique, and are referred to as 'Model I regression'(Cornbleet and Cochrane, 1979; Ludbrook, 1997). A key feature of Model I models is that the independent variable is assumed to be measured without error. As often pointed out in several papers (Altman and Bland, 1983; Ludbrook, 1997), this assumption invalidates simple linear regression for use in method comparison studies, as both methods must be assumed to be measured with error.

The use of regression models that assumes the presence of error in both variables X and Y have been proposed for use instead. (Cornbleet and Cochrane, 1979; Ludbrook, 1997), These methodologies are collectively known as 'Model II regression'. They differ in the method used to estimate the parameters of the regression.

Regression estimates depend on formulation of the model. A formulation with one method considered as the X variable will yield different estimates for a formulation where it is the Y variable. With Model I regression,the models fitted in both cases will entirely different and inconsistent. However with Model II regression, they will be consistent and complementary.

Regression approaches are useful for a making a detailed examination of the biases across the range of measurements, allowing bias to be decomposed into fixed bias and proportional bias. Fixed bias describes the case where one method gives values that are consistently different to the other across the whole range. Proportional bias describes the difference in measurements getting progressively greater, or smaller, across the range of measurements. A measurement method may have either an attendant fixed bias or proportional bias, or both. (**?**). Determination of these biases shall be discussed in due course.

0.1.1 Simple Linear Regression

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

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

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

0.1.2 Deming Regression

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

Deming regression is a regression fitting approach that assumes error in both variables. Deming regression is recommended by Cornbleet and Cochrane (1979) as the preferred Model II regression for use in method comparison studies. The sum of squared distances from measured sets of values to the regression line is minimized at an angles specified by the ratio λ of the residual variance of both variables. I When λ is one, the angle is 45 degrees. In ordinary linear regression, the distances are minimized in the vertical directions (Linnet, 1999).

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

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

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

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

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

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

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

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

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

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

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

Table 1: Transmitral volumetric flow(MF) and left ventricular stroke volume (SV) in 21 patients. (Zhang et al 1986)

0.1.3 Deming's Regression

The most commonly known Model II methodology is known as Deming's Regression, (also known an Ordinary Least Product regression). Deming regression is recommended by Cornbleet and Cochrane (1979) as the preferred Model II regression for use in method comparison studies. As previously noted, the Bland Altman Plot is uninformative about the comparative influence of proportional bias and fixed bias. Deming's regression provides independent tests for both types of bias.

For a given λ, Kummel (1879) derived the following estimate for the Demimg regression slope parameter. (α is simply estimated by using the identity $\bar{Y} - \hat{\beta}\bar{X}$.)

$$\hat{\beta} = \frac{S_{YY} - \lambda S_{XX} + [(S_{YY} - \lambda S_{XX})^2 + 4\lambda S_{XY}^2]^{1/2}}{2S_{XY}} \tag{2}$$

As with conventional regression methodologies, Deming's regression calculates an estimate for both the slope and intercept for the fitted line, and standard errors thereof. Therefore there is sufficient information to carry out hypothesis tests on both estimates,

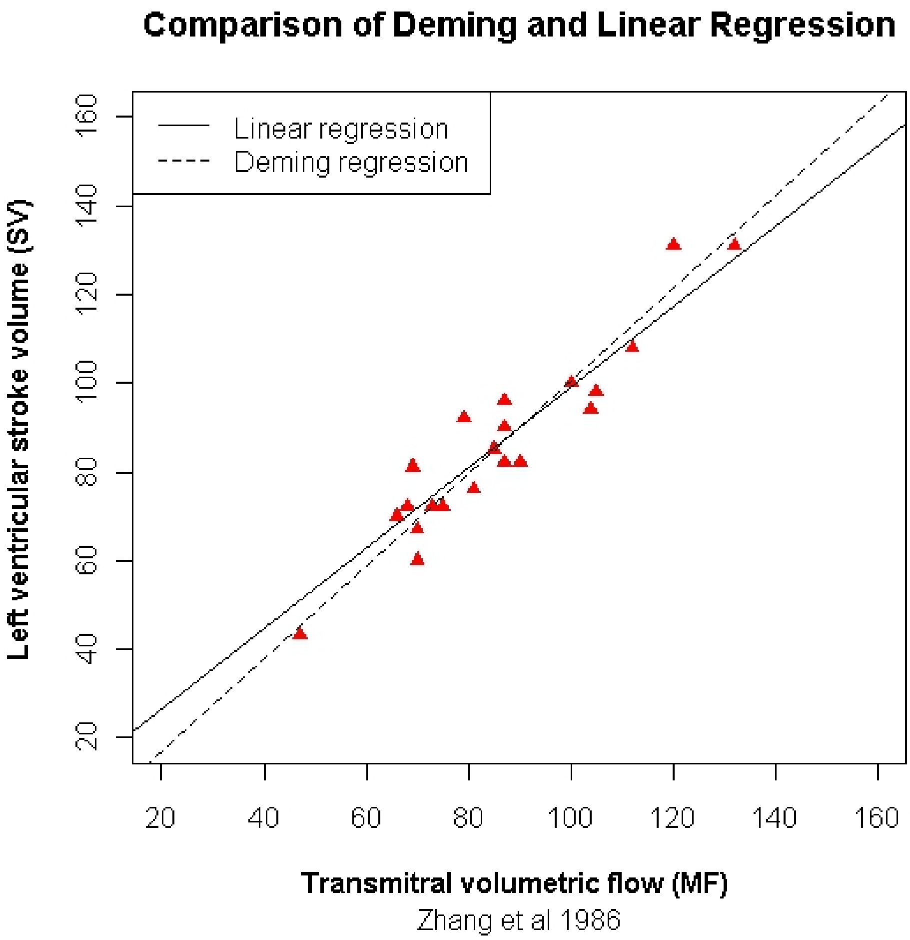

Figure 1: Deming Regression For Zhang's Data

that are informative about presence of fixed and proportional bias.

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

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

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

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1	47	43	8	75	72	15	90	82
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5	70	60	12	87	82	19	112	108
6	70	67	13	87	90	20	120	131
7	73	72	14	87	96	21	132	131

Table 2: Transmitral volumetric flow(MF) and left ventricular stroke volume (SV) in 21 patients. (Zhang et al 1986)

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.

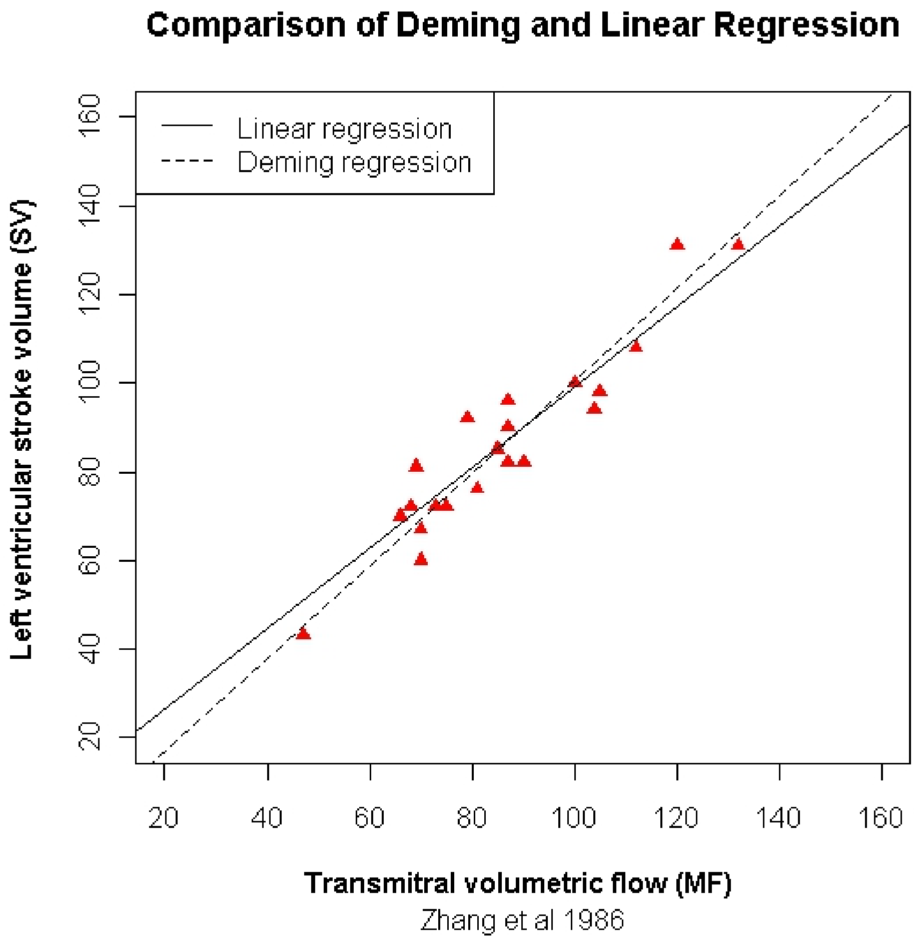

Figure 2: Deming Regression For Zhang's Data

Deming Regression

- Informative analysis for the purposes of method comparison, Deming Regression is a regression technique taking into account uncertainty in both the independent and dependent variables.

- Demings method always results in one regression fit, regardless of which variable takes the place of the predictor variables.

- The measurement error (lambda or λ) is specified with measurement error variance related as

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

(where σ_x^2 and σ_y^2 is the measurement error variance of the x and y variables, respectively).

- In the case where λ is equal to one, (i.e. equal error variances), the methodology is equivalent to ***orthogonal regression***.
- Deming approaches the matter by simultaneously minimizing the sum of the square of the residuals of both variables. This derivation results in the best fit to minimize the sum of the squares of the perpendicular distances from the data points.
- To compute the slope by Demings formula, normally distributed error of both variables is assumed, as well as a constant level of imprecision throughout the range of measurements.

0.2 Model II Regression

0.2.1 Model II regression

Cochrane and Cornbleet argue for the use of methods that based on the assumption that both methods are imprecisely measured ,and that yield a fitting that is consistent with both 'X on Y' and 'Y on X' formulations. These methods uses alternatives to the OLS approach to determine the slope and intercept.
They describe three such alternative methods of regression; Deming , Mandel, and Bartlett regression. Collectively the authors refer to these approaches as Model II regression techniques.

0.2.2 Contention

Several papers have commented that this approach is undermined when the basic assumptions underlying linear regression are not met, the regression equation, and consequently the estimations of bias are undermined. Outliers are a source of error in regression estimates.In method comparison studies, the X variable is a precisely measured reference method. Cornbleet Gochman (1979) argued that criterion may be regarded as the correct value. Other papers dispute this.

0.2.3 Least Product Regression

Least Product Regression , also known as 'Model II regression' caters for cases in which random error is attached to both dependent and independent variables. Ludbrook cites this methodology as being pertinent to Method comparison studies.

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 considered suitable for calibrating one method against another.Ludbrook comments that it is also a sensitive technique for detecting and distinguishing fixed and proportional bias between methods.

Proposed as an alternative to Bland & Altman methodology ,this method is also known as 'Geometric Mean Regression' and 'Reduced Major Axis Regression'. Evaluation of Regression Procedures for Methods Comparison Studies Kristian Linnet

Comparison of Two Clinical Chemistry Methods by Regression Analysis

$$x_i = X_i + \varepsilon_i$$

$$y_i = Y_i + \delta_i$$

Passing and Bablok Performance of Regression Methods RMSE

Outliers and Non-Gaussian Error Distributions

Application of Deming Regression

Squared Analytical Error Ratio λ

Bias of the Slope Estimate

Estimation of the Deming Regression Line

$$\beta_{OLR} = \frac{\beta}{1 + \frac{SD^2_{ax}}{SD^2_X}}$$

0.2.4 Difference with Least Squares Regression

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).

Deming regression

The Deming regression line is estimated by minimizing the sums of squared deviations in both the x and y directions at an angle determined by the ratio of the analytical standard deviations for the two methods. This ratio can be estimated if multiple measurements were taken with each method, but if only one measurement was taken with each method, it can be assumed to be equal to one.

Deming Regression

Performance of Deming regression analysis in case of misspecified analytical error ratio in method comparison studies

Application of Deming regression analysis to interpret method comparison data presupposes specification of the squared analytical error ratio (λ, but in cases involving only single measurements by each method, this ratio may be unknown and is often assigned a default value of one.

On the basis of simulations, this practice was evaluated in situations with real error ratios deviating from one. Comparisons of two electrolyte methods and two glucose methods were simulated.

In the first case, misspecification of λ produced a bias that amounted to two-thirds of the maximum bias of the ordinary least-squares regression method. Standard errors and the results of hypothesis-testing also became misleading. In the second situation, a misspecified error ratio resulted only in a negligible bias.

Thus, given a short range of values in relation to the measurement errors, it is important that λ is correctly estimated either from duplicate sets of measurements or, in the case of single measurement sets, specified from quality-control data. However, even with a misspecified error ratio, Deming regression analysis is likely to perform better than least-squares regression analysis.

Fiducial approach for assessing agreement between two instruments

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This paper presents an approach for making inferences about the intercept and slope of a linear regression model when both variables are subject to measurement errors. The approach is based on the principle of fiducial inference. A procedure is presented for computing uncertainty regions for the intercept and slope that can be used to assess agreement between two instruments. Computer codes for performing these calculations, written using open-source software, are listed.

EQUIVALENCE REGION

The equivalence region is specified by the user. It can be an ellipse, parallelogram, rectangle, or a region of some other appropriate shape. The way we use the fiducial region in this method is as follows. If the 1γ fiducial region that we construct is completely inside the equivalence region then we have established agreement.

maximum allowable difference of the two equivalent methods.

In this paper we have provided an approach for making inference on the intercept β_0 and slope β_1 of a linear regression model with both X and Y subject to measurement errors. Specifically, we have provided procedures for constructing uncertainty regions for $(\beta_0, \beta_1\ )$ that can be used to assess agreement between two methods. The approach is based on fiducial inference.

Koning

http://www.springerlink.com/content/r1063462u618q483/

Use of deming regression in method comparison studies. Henk Konings

- Accuracy is closeness to the true value, or alternatively, having a low measurement error.
- The determination of a true value for a biological specimen is difficult and sometimes impossible.
- Precision is expressed in terms of standard deviation, coefficient of variance or variance.
- In Deming regression, the errors between methods are assigned to both methods in proportion to the variances of the methods.

0.3 Linnet - References

The statistical procedures are described in: Linnet K. Necessary sample size for method comparison studies based on regression analysis. Clin Chem 1999; 45: 882-94. Linnet K. Performance of Deming regression analysis in case of misspecified analytical error ratio in method comparison studies. Clin Chem 1998; 44: 1024-1031. Linnet K. Evaluation of regression procedures for methods comparison studies. Clin Chem 1993; 39. 424-432. Linnet K. Estimation of the linear relationship between measurements of two methods with proportional errors. Stat Med 1990; 9: 1463-1473.

0.4 Implementation of Deming Regression with `Rs`

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.

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