A Direct Comparison of Two Slope-Estimation Techniques Used in Method-Comparison Studies

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Least-squares regression estimation of the slope and intercept in method-comparison studies is the most common method of data evaluation despite well known theoretical difficulties with this approach. An alternative estimation technique has been suggested, which avoids some of these theoretical difficulties. I developed an exact mathematical relationship between these two slope estimates in order to directly compare their characteristics. A simple approximate formula for the relative difference between the two slope estimates is also derived. Using these mathematical relationships, I compare the two estimation techniques, using data from published method-comparison studies. In most of the published method comparisons the differences between slope estimates were trivial, but in some the differences were large enough to have warranted use of the alternative slope estimate.

Several published articles allude to the potential problems associated with the least-squares regression technique for estimating the slope and intercept of the linear relationship between two analytical methods (1-3). Violation of the assumption that one of the analytical methods being compared is error free results in a least-squares slope estimate that tends to be too small. An alternative procedure (Deming's modification) for estimating the slope and intercept has been suggested, which does not require the assumption that one of the analytical methods is error free (1, 2). When information is available as to the relative precision of two analytical methods, this technique gives a more nearly accurate estimate of the true slope.

In spite of these theoretical considerations, least-squares regression continues to be the most commonly applied estimation technique in method-comparison studies. Possible reasons for this include lack of awareness of an alternative to least-squares regression, lack of understanding regarding how to implement the alternative procedure, or a belief that the difference between the two estimates is unimportant. The purpose of this paper is to present a direct comparison of the two estimation techniques, in order to show how they relate mathematically as well as to illustrate the magnitude of the differences in the calculated slopes that can occur in typical method-comparison settings.

References

Methods

The linear relationship between two analytical methods can be defined as:

\[ Y = \alpha + \beta X \]

Estimates are obtained from a set of measured values \((x, y)\) related to the true values \((X, Y)\) by

\[ y = Y + \epsilon \]
\[ x = X + \delta \]

where \(\epsilon\) and \(\delta\) denote the measured errors associated with method \(Y\) and \(X\).

The ordinary linear regression model assumes method \(X\) is error free, implying \(\delta = 0\). The least-squares estimates for \(\alpha\) and \(\beta\) (denoted \(b_{LS}\) and \(b_{LS}\)) are obtained by minimizing the sum of the squared deviations in the \(Y\) direction of the observed data points from the estimated line. Many pocket calculators now have special function keys for the direct calculation of the least-squares slopes, intercept, and the correlation coefficient, \(r\).

The linear functional-relationship model generalizes the linear regression model by allowing \(\delta\) to be nonzero. Two approaches to estimating \(\alpha\) and \(\beta\) are common in the statistical literature: the maximum likelihood estimator and the generalized least-squares estimator. When the errors \(\epsilon\) and \(\delta\) are assumed to be independently distributed with constant variances at a fixed ratio, both approaches yield the same estimates \((4)\). The equation for the slope estimate (it is called "Deming's slope" in 1 and 2, but it will be referred to as the "linear functional slope estimate" here) can be written as:

\[ b_{LF} = \frac{(s^2 - \lambda s^2)^+ + ((s^2 - \lambda s^2)^2 + 4\lambda s^2)^{1/2}}{2 s_{xy}} \]

where

\[ \lambda = \text{variance due to } \epsilon/\text{variance due to } \delta \]

and \(s_{xy}\), \(s^2\), and \(s^2\) denote the sample covariance, variance of \(x\), and variance of \(Y\), respectively.

Both techniques estimate the intercept as

\[ a = \bar{y} - b \bar{x} \]

Hence, the relationship between the two intercept estimates will be reflected in the relationship between the slope estimates and will not be considered further.

The two slope estimates can be directly compared by reformulating the linear functional slope in terms of the least-squares slope. After algebraic substitution and reorganization, the linear functional slope can be written as:

\[ b_{LF} = 1/2 \left\{ \frac{b_{LS}}{\chi^2} - \frac{\lambda}{b_{LS}} + \left[ \frac{b_{LS}}{\chi^2} - \frac{\lambda}{b_{LS}} + 4\lambda \right]^{1/2} \right\} \]

Equation 6 defines the precise relationship between \(b_{LF}\) and \(b_{LS}\) for a given value of \(r\) and \(\lambda\).

In order to get an idea of the kinds of differences between \(b_{LF}\) and \(b_{LS}\) that can occur in typical method-comparison settings, I surveyed nine consecutive issues of Clinical Chemistry for method-comparison studies that reported a slope estimate and correlation coefficient. Articles where the estimated linear relationship seemed to be of only minor or tangential importance to the purpose of the article were not included. Frequently, authors did not indicate how the slope and intercept were calculated. In such cases, it is assumed that least-squares regression estimates are being reported, as is the current journal policy \((5)\). Only one study in the nine issues I surveyed indicated that a linear functional estimation approach had been used.

All calculations for this work were performed with a Digital Equipment Corporation PDP 11/24 computer. Plots were generated on a Hewlett Packard 7470A digital x-y plotter.

Results

Mathematical evaluation of equation 6 confirms the following observations:

- \(b_{LF}\) is always greater than \(b_{LS}\)
- as \(\lambda\) becomes very large, \(b_{LF}\) approaches \(b_{LS}\)
- as \(\lambda\) becomes very small, \(b_{LF}\) approaches \(b_{LS}/\chi^2\), which is equal to the inverse of the least-squares slope estimate that would have been obtained if the axes had been reversed
- as \(r\) decreases, the difference between \(b_{LF}\) and \(b_{LS}\) increases
- the difference between \(b_{LF}\) and \(b_{LS}\) is most sensitive to the value of \(\lambda\) when \(\lambda\) is near 1.0.

These relationships are illustrated in Figure 1, where \(b_{LF}\) is plotted as a function of \(\lambda\) for various values of \(r\), with \(b_{LS}\) set to 0.95.

Sixty-six method comparisons were identified in the nine-month survey of Clinical Chemistry. The sample sizes of the method comparisons ranged from 18 to 456, with a median of 58. The least-squares slope estimates ranged from 0.684 to 1.6 with a median of 0.975. The sample correlation coefficients ranged from .813 to .9999, with a median of .974.

Calculation of \(b_{LF}\) from equation 6 requires a value for \(\lambda\). Rarely were precision data for both analytical methods reported; however, in many method-comparison situations it is reasonable to expect that \(\lambda\) will be near 1.0. Setting \(\lambda = 1.0\), I calculated \(b_{LF}\) for all of the 66 method comparisons, and Figure 2 plots the values of \(b_{LF}\) vs \(b_{LS}\) for each. The difference between the slope estimates averaged 0.034. In 48 (73%) of the method comparisons, the difference between the two slope estimates was less than 0.05. In 16 (24%), the difference was between 0.05 and 0.10, and in two cases (3%) the difference exceeded 0.10. Note that all points fall above the line with slope = 1 and intercept = 0.

The size of the differences between \(b_{LF}\) and \(b_{LS}\) is related to \(r\). The points plotted in Figure 2 represent method comparisons with a range of values for \(r\). In Figure 3 the relative difference between the slopes, RD = \((b_{LF} - b_{LS})/b_{LF}\), is plotted as a function of \(r\) for each method comparison.

![Fig. 1. Relationship between the linear functional slope estimate, \(b_{LF}\), and the least-squares slope estimate as a function of the relative precision between analytical methods, \(\lambda\), for different values of the coefficient of correlation between analytical methods, \(r\). The curves were calculated from equation (6), with the least-squares slope, \(b_{LS}\), set to 0.95 (dashed line).](image-url)
two solid curves in Figure 3 define the exact relative difference between \( b_{LF} \) and \( b_{LS} \) as a function of \( r \), when equation 6 is used with \( b_{LS} = 0.8 \) and 1.2. Because the curve is very slight, a straight line approximation to these curves will closely approximate values of \( r \) near 1.0. Approximating RD with a linear function of \( r \) (using a Taylor series expansion about \( r = 1.0 \)) gives the equation:

\[
RD = \frac{2b_{LS}^2}{\lambda + b_{LS}^2} (1 - r)
\]

When \( b_{LS} \) and \( \lambda \) are equal to 1.0, equation 7 reduces to

\[
RD = 1 - r
\]

Equation 8 is the dashed line plotted in Figure 3. It provides a very reasonable, yet simple, approximation to the relative difference between the slope estimates. This is the case because (a) most of the method comparisons had least-squares slope estimates near 1.0, (b) \( \lambda \) was set to 1.0 in each case, and (c) the linear approximation is very good for values of \( r \) greater than .90. It can be seen that the surveyed method comparisons tend to cluster about the dashed line.

The relative precision, \( \lambda \), was set to 1.0 in the computations performed above, because for many method comparisons, values near 1.0 will be typical. However, nothing precluded substituting other values for \( \lambda \). From equation 7 it can be seen that if \( \lambda = 4.0 \) had been used (implying that method Y has twice as large a coefficient of variation as method X), the differences would have tended to be about 40% as large as the differences plotted in Figures 2 and 3. If \( \lambda \) had been set to 0.25 (method X with twice the coefficient of variation of method Y) the differences would have been about 60% greater than those plotted.

**Discussion**

The implications of the choice of slope estimation technique in a method-comparison study depend on the relative precision between the analytical methods being compared and the correlation between the methods. When \( \lambda \) is large (e.g., \( \lambda > 25 \), which implies that the coefficient of variation for method Y is five times that for method X) then the two slope estimates will be very similar, even when the correlation between analytical methods is relatively low. Also, when the correlation is high \( (r > .99) \) the estimates will be very similar regardless of the value of \( \lambda \). However, when the correlation is more moderate, the relative precision between analytical methods becomes an important factor. If \( .90 < r < .95 \) and \( \lambda \) is on the order of 1.0, then the least-squares slope estimate will tend to be 5 to 10% smaller than the linear functional slope estimate. If the analytical methods have different precision and they are plotted with the less precise method defined as the independent variable, so that \( \lambda \) may be substantially less than 1.0, then even larger differences between the slope estimates could be expected.

The survey of Clinical Chemistry suggests that in most cases the correlation between analytical methods is high enough that the differences between the two slope estimates is trivial. However, in some cases the magnitude of the difference between the slope estimates warrants consideration of the linear functional estimation procedure. The linear functional slope and intercept estimates should be reported in any situation where two analytical methods are being compared and (a) the correlation between methods is less than .95 and (b) the methods are of approximately equal precision, or the method being designated the independent variable X is less precise than the method being designated the dependent variable Y. Equation 6 provides an easy formula for the direct computation of the linear functional slope estimate once the least-squares slope and correlation have been calculated.

Finally, it is worth noting that the proper regression procedure, even when both variables are subject to measurement error, is not always the Deming procedure, but depends essentially on the objectives of the investigator. For example, if Method X is a current procedure and Method Y is a newly proposed method, one may be interested in predicting the y-value for observed x. In this case, ordinary LS regression of y on x is correct even if x is not the true value because of measurement error. Often, both regression estimates will be useful for the same set of data because they serve quite different purposes, both of which may be appropriate for a given set of data. Technically speaking, the linear functional problem is not a regression problem at all, but an estimation of the linear relationship between two expected values.

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Relationship of Potassium and Magnesium Concentrations in Serum to Cardiac Arrhythmias

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Low concentrations of potassium and magnesium in serum have been implicated in cardiac arrhythmias; the importance of mild hypokalemia or hypomagnesemia is uncertain. To investigate possible associations among use of diuretics, the concentration of these ions in serum, and the onset of clinically important arrhythmias, we reviewed records of 103 patients admitted to our Coronary Care Unit during three months and found mild to moderate hypokalemia and hypomagnesemia in 18 and 24%, respectively. The significant correlation between the concentrations of magnesium and potassium in serum at admission (r = 0.27, p < 0.007) remained constant in patients, whether they were receiving diuretics or not. Potassium concentrations were significantly lower (p < 0.05) in patients receiving diuretics (3.93 mmol/L) than in those who were not (4.21 mmol/L), but the mean concentrations of magnesium did not differ significantly. Except for myocardial infarction, no single variable or combination of variables was highly predictive of cardiac arrhythmias in these patients. We conclude that there is no strong predictive relationship between mildly decreased concentrations of magnesium or potassium in serum and onset of cardiac arrhythmias.

Additional Keyphrases: risk factors • hypokalemia • hypomagnesemia • myocardial infarction • hypertension • coronary-care units • diuretics • heart disease • discriminant analysis

Low concentrations of potassium and magnesium in serum have been implicated in the etiology of cardiac arrhythmias (1–3), but the potential role of mild decreases in the concentrations of these ions remains controversial (4, 5). Of particular interest has been the question of whether the mild degrees of hypokalemia and hypomagnesemia induced by diuretic therapy constitute a significant risk in patients being treated with these agents for hypertension. Several studies suggest that diuretic-induced hypokalemia is of little consequence clinically and that potassium supplementation is not needed routinely for most such patients (4–7). A recent report from the American Multiple Risk Factor Intervention Trial (8), however, presented evidence that therapy with thiazide diuretics may have increased the death rate from coronary heart disease (including sudden death) in hypertensive men who had abnormalities in their electrocardiograms taken while resting, possibly by causing arrhythmias.

Because several reports (e.g., 2, 3, 9, 10) have suggested that the potential for mild hypokalemia and hypomagnesemia to lead to arrhythmias may be greater after myocardial infarction, we studied a series of patients admitted consecutively to the Coronary Care Unit and attempted to identify possible relationships among the use of diuretics, mild hypokalemia and hypomagnesemia, and the occurrence of clinically significant arrhythmias.

Materials and Methods

We gathered our data from the charts for 103 of 113 consecutive patients admitted to our institution's Coronary Care Unit during a three-month period. (Charts for the remaining 10 patients could not be located for study.) For each patient we recorded age and sex; historical evidence of congestive heart failure, hypertension, and diuretic therapy; the serum concentrations of magnesium and potassium at admission; and the final clinical diagnosis as to whether the patient had had a myocardial infarction. To measure concentrations of potassium in serum we used ion-selective electrodes, in either the SMAC (Technicon Corp., Tarrytown, NY 10591) or the Astra-8 (Beckman Instruments, Inc., Brea, CA 92621) analyzers; routine quality-control comparisons of the results obtained for serum with these two instruments did not differ significantly. Magnesium in

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