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An exact test for analytical bias detection

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Abstract

In this paper a simple exact test statistic to detect analytical bias is proposed. The test requires neither specialized software nor iterative procedures. Comparisons with an asymptotic test using simulation studies show that the proposed test presents good behavior in terms of significance level and power. Applications to a real data set are also reported. Some general guidelines concerning the choice of the test to be used are discussed.

Keywords: Analytical bias; Hypothesis tests; Exact test; Wald test

1. Introduction

Regression analysis is a technique widely applied in comparing two analytical methods at several concentration levels [1,2]. Frequently two methods are compared on a range of specimen whose concentration levels are not known precisely. It is considered that the methods are error prone and the variances of the measurement errors in both methods are not constant throughout the concentration levels and are assumed as known. Several approaches have been used with validation processes involving two methods (an “old” or reference and a “new” method). Riu and Rius [3] comment on some pitfalls of the ordinary and weighted least square techniques, and advocate the use of bivariate least squares [4]. Bias in the new method is tested using an elliptical joint confidence region for the intercept and slope parameters. Another alternative is found in Ripley and Thompson [5], where it is assumed that the measurement errors follow normal (Gaussian) distributions, propose to estimate the intercept and the slope parameters by maximum likelihood under a functional model. These authors also propose separate tests for testing null intercept and unit slope. In a paper recently published, Galea-Rojas et al. [6] set the problem in a functional errors-in-variables modeling framework and under normality of the errors, maximum likelihood estimation of the parameters is achieved through simple iterative steps. Moreover, a Wald type statistic which guarantees correct asymptotic significance levels to test the unbiasedness of the new measurement device is also proposed.

In the present work, a careful appraisal of the model enables deriving an exact test to detecting analytical bias in the new method. According to the results in Section 2, the proposed test has a simple form and is simple to use in the sense that it does not require computing parameter estimates. Results of simulation studies reported in Section 3 show a good agreement between empirical and theoretical significance levels and a satisfactory behavior in terms of power. A real data application of the Wald (in [6]) and the exact tests are reported in Section 3.

2. Theory

Let n be the number of samples analyzed; X_i, the concentration value observed by using the old method in sample i; Y_i,

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the concentration value observed by using the new method in sample i; x_i, the unobserved reference (true) concentration value for sample i, $i = 1, \ldots, n$. Relating the above variables, we consider the functional errors-in-variables model [5,6]

$$X_i = x_i + u_i \quad (1)$$

$$Y_i = \alpha + \beta x_i + e_i \quad (2)$$

$i = 1, \ldots, n$. In Eq. (2), α and β can be seen as additive and multiplicative biases of the new method (method 2) with respect to the old method (method 1). We assume that the measurement errors u_i and e_i are independent (their covariance is null) and follow a bivariate normal distribution with known variances κ_i and λ_i, $i = 1, \ldots, n$. This issue deserves a commentary. In many applications reviewed in the literature, values for the variances are obtained from replicating the sample units. For instance, in a comparative study of mercury determination [7], the data pairs and their respective variances are generated from six replicates performed at each point. In a comparison of formaldehyde measurement methods [2], three levels of concentration were selected (in the middle and at the extremes of the concentration range). At each level, fifteen pairs of measurements generate estimates of the common error variances. Indeed, a more general formulation, accounting for a direct modeling of the variances as functions of the true measurements, could be envisioned.

Hence, the observable vectors

$$\begin{pmatrix} X_i \\ Y_i \end{pmatrix}$$

are independent and distributed according to a bivariate normal distribution with mean vector

$$\begin{pmatrix} x_i \\ \alpha + \beta x_i \end{pmatrix}$$

and variances κ_i and λ_i, $i = 1, \ldots, n$.

The absence of bias in the new method is expressed by the hypothesis

$$H_0 : \begin{pmatrix} \alpha \\ \beta \end{pmatrix} = \begin{pmatrix} 0 \\ 1 \end{pmatrix} \quad (3)$$

Maximum likelihood estimation of α and β through simple iterative steps, as well as a Wald type statistic to test the hypothesis in Eq. (3) are discussed in Galea-Rojas et al. [6]. This statistic assures correct asymptotic significance levels taken from a chi-square distribution with two degrees of freedom. The reader is referred to this paper for a complete account of the matter.

On the other hand, it follows from (1) and (2) that

$$E(Y_i - \alpha - \beta X_i) = 0, \qquad \mathrm{var}(Y_i - \alpha - \beta X_i) = \lambda_i + \beta^2 \kappa_i$$

so that

$$\frac{Y_i - \alpha - \beta X_i}{(\lambda_i + \beta^2 \kappa_i)^{1/2}}$$

follows a standard normal distribution and are independent, $i = 1, \ldots, n$, implying that

$$Z = n^{-1/2} \sum_{i=1}^{n} \frac{Y_i - \alpha - \beta X_i}{(\lambda_i + \beta^2 \kappa_i)^{1/2}} \quad (4)$$

also follows a standard normal distribution. This is a key result, because the distribution of Z does not depend on α and β (in statistical parlance, Z is called a pivotal quantity).

Therefore, the set of points

$$\{(\alpha, \beta) \in \mathbb{R}^2 : |Z| \leq z_{1-\gamma/2}\} \quad (5)$$

provides a $(1 - \gamma) \times 100\%$ exact confidence region for (α, β), where $z_{1-\gamma/2}$ is the $(1 - \gamma/2)$ upper quantile of the standard normal distribution. When $\kappa_i = \kappa$ and $\lambda_i = \lambda$, $i = 1, \ldots, n$, equality in Eq. (5) defines a hyperbola. The confidence region is the strip between the two curves of the hyperbola, as depicted in Fig. 1.

To test the null hypothesis in Eq. (3) of no biases in the new method, we select a significance level (γ = 10 or 5%, say), compute Z in Eq. (4) with $\alpha = 0$ and $\beta = 1$ resulting in

$$Z_0 = n^{-1/2} \sum_{i=1}^{n} \frac{Y_i - X_i}{(\lambda_i + \kappa_i)^{1/2}} \quad (6)$$

and if $|Z_0| \leq z_{1-\gamma/2}$, we do not reject H_0. In an equivalent way, H_0 is not rejected if the point (0, 1) belongs to the region delimited by Eq. (5). This procedure generalizes a test proposed by [8, Section 2.4.3]. Confidence region in Eq. (5) is unbounded. This does not impose a hindrance, because our main interest is the test of no biases in the new method.

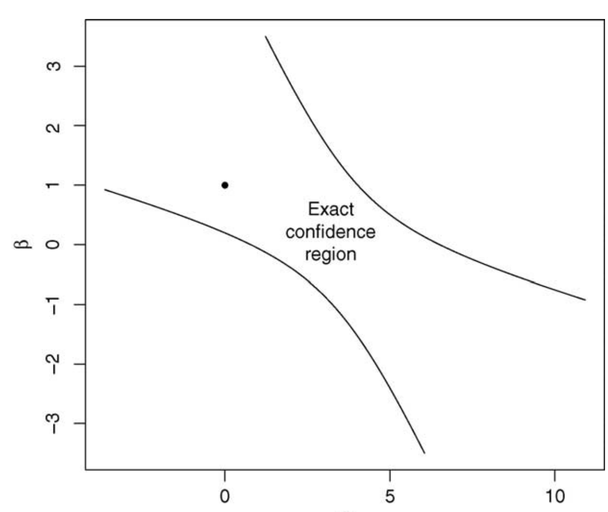

Fig. 1. Exact confidence region for (α, β) in the model with constant error variances and the point representing absence of bias in the new method.