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# Hyperbolic confidence bands of errors-in-variables regression lines applied to method comparison studies

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**Abstract:** This paper focuses on the confidence bands of errors-in-variables regression lines applied to method comparison studies. When comparing two measurement methods, the goal is to 'proof' that they are equivalent. Without analytical bias, they must provide the same results on average notwithstanding the errors of measurement. The results should not be far from the identity line $Y = X$ (slope $(\beta)$ equal to 1 and intercept $(\alpha)$ equal to 0). A joint-CI is ideally used to test this joint hypothesis and the measurement errors in both axes must be taken into account. DR (Deming Regression) and BLS (Bivariate Least Square regression) regressions provide consistent estimated lines (confounded under homoscedasticity). Their joint-CI with a shape of ellipse in a $(\beta,\alpha)$ plane already exist in the literature. However, this paper proposes to transform these joint-CI into hyperbolic confidence bands for the line in the $(X,Y)$ plane which are easier to display and interpret. Four methodologies are proposed based on previous papers and their properties and advantages are discussed. The proposed confidence bands are mathematically identical to the ellipses but a detailed comparison is provided with simulations and real data.When the error variances are known, the coverage probabilities are very close to each other but the joint-CI computed with the maximum likelihood (ML) or the method of moments provide slightly better coverage probabilities. Under unknown and heteroscedastic error variances, the ML coverage probabilities drop drastically while the BLS provide better coverage probabilities.

**Résumé :** Cet article se concentre sur la construction et l'évaluation de la qualité de bandes de confiance de droites de régression à erreurs sur les variables utilisées dans le contexte particulier de la comparaison de méthodes de mesure. La comparaison de méthodes de mesure vise à vérifier, sur base de données expérimentales, que deux méthodes de mesure fournissent des résultats équivalents. En l'absence de biais analytique, deux méthodes, entachées d'erreurs de mesure, doivent fournir des résultats en moyenne identiques, c'est-à-dire distribués autour de la droite $Y = X$ de pente $(\beta)$ égale à 1 et d'ordonnée à l'origine $(\alpha)$ égale à 0. Pour tester cette hypothèse, un intervalle de confiance (IC) joint est idéalement utilisé en tenant compte des erreurs de mesure sur les deux axes. Les régressions DR (Régression de Deming) et BLS (Bivariate Least Square regression) fournissent des droites de régression consistantes et confondues sous homoscédasticité. Leurs IC joints sous forme d'ellipses dans un plan $(\beta,\alpha)$ sont présentés et cet article propose de transformer ces IC joints en des bandes de confiance hyperboliques pour la droite dans le repère $(X,Y)$ qui sont plus faciles à mettre en graphique et à interpréter par le praticien. Quatre méthodes pour les calculer sont proposées et leurs propriétés et avantages respectifs discutés. Une comparaison détaillée est fournie basée, entre autre, sur des simulations et des données réelles. Lorsque les variances des erreurs sont connues, les taux de couverture sont semblables, mais les IC joints calculés avec le maximum de vraisemblance (ML) ou la méthode des moments fournissent des taux de couverture légèrement meilleurs. Quand les variances des erreurs sont inconnues et hétéroscédastiques, les taux de couverture du ML chutent de façon spectaculaire tandis que le BLS donne des meilleurs taux de couverture.

***Keywords:*** confidence bands, errors-in-variables regression, method comparison study, equivalence of measurement methods, deming regression, bivariate least square

***Mots-clés :*** bandes de confiance, régression avec erreurs sur variables, comparaison de méthode, équivalence de méthode de mesure, régression deming

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## 1. Introduction

The needs of the industries to quickly assess the quality of products leads to the development and improvement of new measurement methods sometimes faster, easier to handle, less expensive or more accurate than the reference method. These alternative methods should ideally lead to results comparable to those obtained by a standard method (Westgard and Hunt, 1973) in such a way that there is no bias between these two methods or that these measurement methods can be interchangeable.
Different approaches are proposed in the literature to deal with the method comparison studies. Firstly, the most known and widely used is certainly the approach proposed by Bland and Altman which focuses directly on the differences between two measurement methods (Altman and Bland, 1983; Bland and Altman, 1986, 1999). Secondly, the approach based on regression analysis (or linear functional relationship (Lindley, 1947)) is also widely applied and focuses on the regression parameter estimates and their CI (confidence intervals) (Martínez et al., 1999). Each approach has its own advantages and disadvantages, the first being more intuitive for the user and the second providing a stronger statistical basis. This paper focuses on the regression approach.
To test statistically the equivalence between two measurement methods, a certain characteristic of a sample can be measured by the two methods in the experimental domain of interest. The pairs of measures taken by both methods can be modeled by a linear regression (a straight line). Then, the parameter estimates are very useful to test the equivalence. Indeed, an intercept significantly different from zero indicates a systematic analytical bias between the methods and a slope significantly different from one indicates a proportional bias (Martínez et al., 1999). To achieve this correctly, it is essential to take into account the errors in both axes and the heteroscedasticity if necessary (Martínez et al., 1999). Various types of regressions exist to deal with this problem (Riu and Rius, 1995). The equivalence test is, here, based on the joint-CI which is usually an ellipse. This paper proposes, then, to tranfsorm these classical ellipses into hyperbolic confidence bands for the regression line with replicated or unreplicated data. Other confidence bands (Liu et al., 2008; Liu, 2010) like two straight lines around the estimated line will not be considered. Indeed, hyperbolic curves are the only correct way to fit the distribution of estimated lines.
First, the joint-CI and the confidence bands of the very well-known OLS (Ordinary Least Square) regression will be reviewed, explained and compared. Then, four different errors-in-variables regressions will be compared in order to compute a joint-CI with an ellipse and, then, these ellipses will be tranformed into confidence bands. Non-parametric and bootstrap confidence bands for errors-in-variables regressions are available in the literature (Booth and Hall, 1993) but according to our knowledge, the confidence bands given in this paper are novel.

## 2. The model and the goal of method equivalence testing

### *2.1. What is method equivalence and which data are needed to test it?*

When two devices are available or have been used to perform measurements, we can, of course, wonder whether these two devices are equivalent or not. The literature does not provide a clear and unique definition of the equivalence concept. Statistical equivalence approach will, in priority, test whether the two devices are equivalent notwithstanding the measurement errors or whether there is a bias between the two devices. Additionaly, a statistical test can be performed to compare the accuracies of the two methods, if needed. Practical equivalence approach will not focus on statistical parameters but will consider two methods equivalent when one device can be substituted by the other one without affecting the decision taken from the measurement result. This paper will focus mainly on the statistical question and test whether there is a bias between the two devices. The most classical design in method comparison studies consists of measuring each sample once by both devices. Unfortunately, it is therefore not possible to estimate the measurement errors variances if necessary and a design with replicated data is more suitable. If the accuracy of a reference measurement method (gold standard) is known, each sample can be measured one time by this method and several times by a new method to be able to estimate the variance of the errors of this new method.

### 2.2. *The general model*

To compare two measurement methods, a parameter of interest is measured on $N$ samples $(i = 1, 2, ..., N)$ or subjects by both methods (Madansky, 1959; Barnett, 1970; Fuller, 1987):

$$X_{ij} = \xi_i + \tau_{ij}, \; Y_{ik} = \eta_i + \nu_{ik} \tag{1}$$

$X_{ij}(j = 1, 2, ..., n_{X_i})$ and $Y_{ik}(k = 1, 2, ..., n_{Y_i})$ are the repeated measures for sample $i$ by methods $X$ and $Y$ respectively. Sample $i$ is measured $n_{X_i}$ and $n_{Y_i}$ times by, respectively, methods $X$ and $Y$. The true but unobservable values of the parameter of interest for methods $X$ and $Y$, $\xi_i$ and $\eta_i$, are assumed to be linked by a linear regression (Madansky, 1959; Barnett, 1970; Fuller, 1987):

$$\eta_i = \alpha + \beta \xi_i \tag{2}$$

Note that this assumption can be assessed with a lack of fit test (Passing and Bablok, 1983; Martínez et al., 2000). The measurement errors, $\tau_{ij}$ and $\nu_{ik}$, are supposed to be independent and normally distributed (with constant variances under homoscedasticity):

$$\begin{pmatrix} \tau_{ij} \\ \nu_{ik} \end{pmatrix} \sim iN\left( \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2_{\tau_i} & 0 \\ 0 & \sigma^2_{\nu_i} \end{pmatrix} \right) \tag{3}$$

$X_i$ and $Y_i$ are the means of the repeated measures for a given sample:

$$X_i = \frac{1}{n_{X_i}} \sum_{j=1}^{n_{X_i}} X_{ij} \text{ and } Y_i = \frac{1}{n_{Y_i}} \sum_{k=1}^{n_{Y_i}} Y_{ik} \tag{4}$$

These means are also normally distributed around $\xi_i$ or $\eta_i$:

$$\begin{pmatrix} X_i \\ Y_i \end{pmatrix} \sim iN\left( \begin{pmatrix} \xi_i \\ \eta_i \end{pmatrix}, \begin{pmatrix} \frac{\sigma^2_{\tau_i}}{n_{X_i}} & 0 \\ 0 & \frac{\sigma^2_{\nu_i}}{n_{Y_i}} \end{pmatrix} \right) \tag{5}$$

When the variances $\sigma^2_{\tau_i}$ and $\sigma^2_{\nu_i}$ are unknown, they can be estimated with replicated data. Otherwise, these variances are inestimable. The estimators of $\sigma^2_{\tau_i}$ and $\sigma^2_{\nu_i}$ are given by $S^2_{\tau_i}$ and $S^2_{\nu_i}$:

$$S^2_{\tau_i} = \frac{1}{n_{X_i} - 1} \sum_{j=1}^{n_{X_i}} (X_{ij} - X_i)^2 \text{ and } S^2_{\nu_i} = \frac{1}{n_{Y_i} - 1} \sum_{k=1}^{n_{Y_i}} (Y_{ik} - Y_i)^2 \tag{6}$$

In further sections, the means of $X$ and $Y$ ($\overline{X}$ and $\overline{Y}$), their sums of square ($S_{xx}$ and $S_{yy}$) and cross-product ($S_{xy}$) will also be used:

$$\overline{X} = \frac{1}{N}\sum_{i=1}^{N} X_i \text{ and } \overline{Y} = \frac{1}{N}\sum_{i=1}^{N} Y_i,$$

$$S_{xx} = \sum_{i=1}^{N}(X_i - \overline{X})^2, S_{yy} = \sum_{i=1}^{N}(Y_i - \overline{Y})^2 \text{ and } S_{xy} = \sum_{i=1}^{N}(X_i - \overline{X})(Y_i - \overline{Y}).$$

### 2.3. *The homoscedastic model*

Under homoscedasticity, both measurement methods have a constant accuracy through the domain of interest ($\sigma^2_{\tau_i} = \sigma^2_{\tau}$ and $\sigma^2_{\nu_i} = \sigma^2_{\nu}$ $\forall i$). Moreover, equal number of replicates for a given device ($n_{X_i} = n_X$ and $n_{Y_i} = n_Y$ $\forall i$) is here considered, because the mean measures are regressed ($Y_i$ with respect to $X_i$).
Under homoscedasticity, the variances $S^2_{\tau_i}$ and $S^2_{\nu_i}$ are estimates of $\sigma^2_{\tau}$ and $\sigma^2_{\nu}$ and global estimates for $\sigma^2_{\tau}$ and $\sigma^2_{\nu}$ are given by $S^2_{\tau}$ and $S^2_{\nu}$:

$$S^2_{\tau} = \frac{\sum_{i=1}^{N}(n_{X_i} - 1)S^2_{\tau_i}}{(\sum_{i=1}^{N} n_{X_i}) - N} \text{ and } S^2_{\nu} = \frac{\sum_{i=1}^{N}(n_{Y_i} - 1)S^2_{\nu_i}}{(\sum_{i=1}^{N} n_{Y_i}) - N} \tag{7}$$

With constant number of repeated measures ($n_{X_i} = n_X$ and $n_{Y_i} = n_Y$ $\forall i$), the formulas (7) can be simplified into:

$$S^2_{\tau} = \frac{\sum_{i=1}^{N} S^2_{\tau_i}}{N} \text{ and } S^2_{\nu} = \frac{\sum_{i=1}^{N} S^2_{\nu_i}}{N} \tag{8}$$

### 2.4. *How to test the equivalence?*

If the two measurement methods are equivalent, they should give the same results for a given sample notwithstanding the measurement errors. Therefore, according to the model notations, method equivalence implies that $\xi_i = \eta_i$ $\forall i$ (Martínez et al., 1999; Tan and Iglewicz, 1999). In practice, due to the measurement errors, these parameters are unobservable and the equivalence test will be based on the following regression model:

$$Y_i = \alpha + \beta X_i + \varepsilon_i \text{ with } \varepsilon_i \sim N(0, \sigma^2_{\varepsilon_i}) \text{ and } \sigma^2_{\varepsilon_i} = \frac{\sigma^2_{\nu_i}}{n_{Y_i}} + \beta^2 \frac{\sigma^2_{\tau_i}}{n_{X_i}}, \tag{9}$$

where $\alpha$, the intercept and $\beta$, the slope are estimated respectively by $\hat{\alpha}$ and $\hat{\beta}$. This regression model is applied on the average measures (individual measures cannot be paired). A lot of practitioners wonder which measurement method to assign to the X-axis or Y-axis. Actually, the variables $X$ and $Y$ 'play similar roles' (Anderson, 1976). If the regression line is estimated adequately (by taking into account errors in both axes), the coordinate system should not matter (Wald, 1940).
The estimated parameters $\hat{\alpha}$ and $\hat{\beta}$ provide the information to assess the equivalence. Indeed, an intercept significantly different from 0 means that there is a constant bias between the two

measurement methods. A slope significantly different from 1 means that there is a proportional bias (Martínez et al., 1999). So, the following two-sided hypotheses will be used to test method equivalence:

$$H_0^\alpha : \alpha = 0, H_1^\alpha : \alpha \neq 0 \text{ and } H_0^\beta : \beta = 1, H_1^\beta : \beta \neq 1 \tag{10}$$

The null hypothesis $H_0^\alpha$ is rejected if 0 is not included inside a confidence interval (CI) for $\alpha$ and the null hypothesis $H_0^\beta$ is rejected if 1 is not included inside a CI for $\beta$. However, these tests can also be applied jointly by checking whether the point $(1,0)$ is included or not in a joint-CI for the regression coefficients $\theta = (\alpha, \beta)'$ which is, classically, a confidence ellipse. This paper focuses on this joint hypothesis:

$$H_0 : \theta = (0,1)' \text{ and } H_1 : \theta \neq (0,1)' \tag{11}$$

and proposes simultaneous confidence bands (CB) for the regression line $Y = \alpha + \beta X = x'\theta$ over $X \in (-\infty, \infty)$ where $x = (1, X)'$ which are identical to the confidence ellipses. The hypothesis $H_0 : \theta = (0,1)'$ is rejected if the line $Y = X$ intercepts the CB and not rejected if the line lies inside the CB.

## 3. The OLS regression

This section reviews the results of the classical estimation of a regression line by OLS when $X$ is observed without error. These will be crucial in the development in further sections on errors in variables models. In particular, the not well known concept of confidence bands (CB) around the regression line is reviewed. It is shown that it is equivalent to the joint confidence interval on the regression parameters and that they can both be used for equivalence testing.

### *3.1. Ordinary Least Squares (OLS) regression estimators*

The easiest way to estimate the parameters $\alpha$ and $\beta$ of model (9) under homoscedasticity is to apply the very well known technique of Ordinary Least Squares (Gauss, 1809; Legendre, 1805): OLS. The OLS regression minimizes the sum of squared vertical distances (residuals) between each point and the line as shown in Figure 1. The corresponding parameter estimators are given by the well known following formulas:$\hat{\beta}_{OLS} = S_{xy}/S_{xx}$ and $\hat{\alpha}_{OLS} = \overline{Y} - \hat{\beta}_{OLS}\overline{X}$. Unfortunately, OLS assumes that there is no error given by the measurement method in the X-axis (Cornbleet and Gochman, 1979), i.e., $\tau_{ij}$ are supposed to be equal to zero (or negligible). The corresponding estimates are therefore biased (Cornbleet and Gochman, 1979).

### *3.2. Confidence intervals computed from OLS estimators*

The classical $100(1-\gamma)\%$ CI for $\beta_{OLS}$ and $\alpha_{OLS}$ are symmetric around $\hat{\beta}_{OLS}$ and $\hat{\alpha}_{OLS}$ respectively and are computed as (Dagnelie, 2011):

$$CI(\beta_{OLS}) : \hat{\beta}_{OLS} \pm t_{1-\frac{\gamma}{2}, N-2} S_{\hat{\beta}_{OLS}} \text{ with } S_{\hat{\beta}_{OLS}} = \sqrt{\frac{S^2_{OLS}}{S_{xx}}} \tag{12}$$

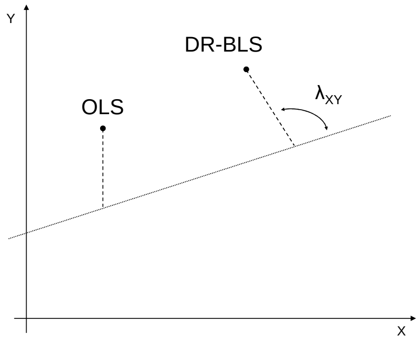


FIGURE 1. *Illustration of OLS and DR-BLS regressions criteria of minimization*

where

$$S^2_{OLS} = \frac{1}{N-2}\sum_{i=1}^{N}(Y_i - \hat{\alpha}_{OLS} - \hat{\beta}_{OLS}X_i)^2,$$

$$CI(\alpha_{OLS}) : \hat{\alpha}_{OLS} \pm t_{1-\frac{\gamma}{2},N-2} S_{\hat{\alpha}_{OLS}} \text{ with } S_{\hat{\alpha}_{OLS}} = \sqrt{S^2_{OLS}\left(\frac{1}{N} + \frac{\overline{X}^2}{S_{xx}}\right)}, \tag{13}$$

where $t_{1-\gamma/2,N-2}$ is the $100(1-\gamma/2)\%$ percentile of a t-distribution with $N-2$ df (degrees of freedom). Additionally, the covariance between the slope and the intercept, $S_{\hat{\alpha}\hat{\beta}_{OLS}}$ is given by:

$$S_{\hat{\alpha}\hat{\beta}_{OLS}} = -\overline{X}\frac{S^2_{OLS}}{S_{xx}} = -\overline{X}S^2_{\hat{\beta}_{OLS}}$$

The joint-CI for $\alpha$ and $\beta$ is, therefore, given by:

$$\begin{pmatrix}\hat{\alpha}_{OLS}-\alpha & \hat{\beta}_{OLS}-\beta\end{pmatrix}\begin{pmatrix}S^2_{\hat{\alpha}_{OLS}} & S_{\hat{\alpha}\hat{\beta}_{OLS}} \\ S_{\hat{\alpha}\hat{\beta}_{OLS}} & S^2_{\hat{\beta}_{OLS}}\end{pmatrix}^{-1}\begin{pmatrix}\hat{\alpha}_{OLS}-\alpha \\ \hat{\beta}_{OLS}-\beta\end{pmatrix} \leq 2F_{1-\gamma,2,N-2}, \tag{14}$$

where $F_{1-\gamma,2,N-2}$ is the $100(1-\gamma)\%$ percentile of the $F$ distribution with 2 and $N-2$ df. This joint-CI is an ellipse centered on the estimated parameters $\hat{\theta} = (\hat{\alpha}_{OLS}, \hat{\beta}_{OLS})'$. When $|S_{\hat{\alpha}\hat{\beta}_{OLS}}|$ increases, the ellipse becomes narrower and collapses to a line, otherwise when $|S_{\hat{\alpha}\hat{\beta}_{OLS}}| \to 0$ the ellipse becomes wider until its major and minor axes become parallel to the $\beta$-axis and $\alpha$-axis. Finally, the equivalence between two measurements methods is rejected if:

$$\begin{pmatrix}\hat{\alpha}_{OLS}-0 & \hat{\beta}_{OLS}-1\end{pmatrix}\begin{pmatrix}S^2_{\hat{\alpha}_{OLS}} & S_{\hat{\alpha}\hat{\beta}_{OLS}} \\ S_{\hat{\alpha}\hat{\beta}_{OLS}} & S^2_{\hat{\beta}_{OLS}}\end{pmatrix}^{-1}\begin{pmatrix}\hat{\alpha}_{OLS}-0 \\ \hat{\beta}_{OLS}-1\end{pmatrix} > 2F_{1-\gamma,2,N-2}.$$

### *3.3. The confidence bands for the OLS line*

The confidence bands for the OLS line is a concept not very well-known by non-statisticians despite many papers already published in the past. Indeed, the confidence band for a line is often not available in classical software. The confidence bands are the CI for the regression line and should not be confused with the CI for the conditional mean $E(\hat{Y}_0|X_0)$ given by the following well-known formula (Dagnelie, 2011):

$$\hat{Y}_0 \pm t_{1-\frac{\gamma}{2},N-2} S_{\hat{Y}_0} \text{ where } \hat{Y}_0 = \hat{\alpha}_{OLS} + \hat{\beta}_{OLS} X_0$$

$$\text{and } S^2_{\hat{Y}_0} = S^2_{\hat{\alpha}_{OLS}} + X_0^2 S^2_{\hat{\beta}_{OLS}} + 2X_0 S_{\hat{\alpha}\hat{\beta}_{OLS}} = S^2_{OLS}\left(\frac{1}{N} + \frac{(X_0-\overline{X})^2}{S_{xx}}\right). \quad (15)$$

This formula is, usually, computed 'point by point' (all possible values of $X_0$) and the results displayed by most of the software on a graph with hyperbolic curves. The CI for the line $Y = \alpha + \beta X$ over $X \in (-\infty, \infty)$ (and not for a given $X_0$) relies on the bivariate dimension of a line by taking into account the uncertainties of both parameters ($\alpha$ and $\beta$) jointly. The confidence bands (CB) of the line $Y = \alpha + \beta X$ under OLS assumptions is given by the following formula [22]:

$$\left(\hat{\alpha}_{OLS} + \hat{\beta}_{OLS} X\right) \pm \sqrt{2F_{1-\gamma,2,N-2}} \sqrt{S^2_{OLS}\left(\frac{1}{N} + \frac{(X-\overline{X})^2}{S_{xx}}\right)}. \quad (16)$$

Both formulas are similar but a F-distribution is used for the confidence bands based on the work of Working and Hoteling (1929).

### 3.4. Comparison of the joint-CI and the confidence bands

Actually, the joint-CI on the regression coefficients and the confidence bands of the regression line are mathematically identical. To test the equivalence between two measurement methods, one can check whether the point ($\beta = 1, \alpha = 0$) lies inside the ellipse or check whether the identity line ($Y = X$) lies inside the confidence bands. Figure 2 (right) displays a simulated data set where the OLS line isestimated and its 95% CB displayed. It can be noticed that the identity line (the dashed line) lies inside the CB which means that the equivalence is not rejected. On the left, the ellipse corresponds to the 95% joint-CI on $(\beta, \alpha)$ and the 'equivalence point' ($\beta = 1, \alpha = 0$) lies within it. More generally, when a given point $(\beta, \alpha)$ lies inside the ellipse, the corresponding line ($Y = \alpha + \beta X$) lies inside the CB and vice-versa. On the other hand, when a given point lies outside the ellipse, the corresponding line intercepts the CB. When a given point is on the edge of the ellipse, the corresponding line is tangent to the CB. Considering all the lines which lie inside the CB, it is obvious that the two extreme slopes correspond to the oblique asymptotes of the hyperbolic CB (red lines in Figure 2-right). These two extreme slopes correspond to the domain of the ellipse (red arrow on Figure 2-left) and these slopes are:

$$\hat{\beta}_{OLS} \pm \sqrt{2F_{1-\gamma,2,N-2}} S_{\hat{\beta}_{OLS}} \quad (17)$$

From the CB, the slopes of the oblique asymptotes can be easily computed:

$$\lim_{X\to\infty} \frac{(\hat{\alpha}_{OLS} + \hat{\beta}_{OLS} X) \pm \sqrt{2F_{1-\gamma,2,N-2}} \sqrt{S^2_{OLS}\left(\frac{1}{N} + \frac{(X-\overline{X})^2}{S_{xx}}\right)}}{X} = \hat{\beta}_{OLS} \pm \sqrt{2F_{1-\gamma,2,N-2}} S_{\hat{\beta}_{OLS}}$$

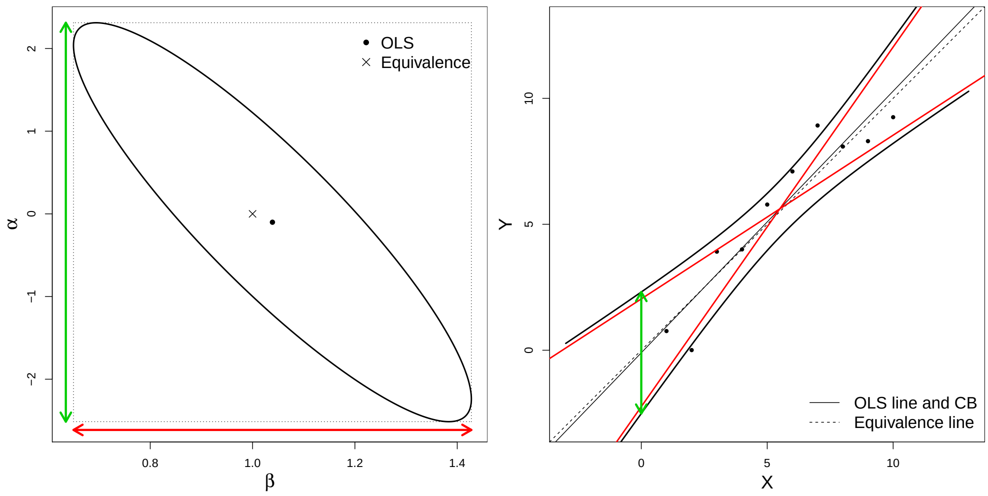


FIGURE 2. *Mathematical equivalence between the joint-CI on $(\beta, \alpha)$ (ellipse on the left) and the CB (hyperbolic band on the right) computed around the estimated line*

By analogy, the image of the ellipse corresponds to the two following extreme intercepts (green arrow in Figure 2-left):

$$\hat{\alpha}_{OLS} \pm \sqrt{2F_{1-\gamma,2,N-2}} S_{\hat{\alpha}_{OLS}}, \tag{18}$$

and correspond to the two intercepts of the CB (when $X = 0$). Finally, for any slope $\beta_0$ in the domain of the ellipse (17), there exists two lines tangent to the hyperbolic CB with slope $\beta_0$ and intercepts $\alpha_0^1$ and $\alpha_0^2$ which correspond on the ellipse, to the two points $\alpha_0^1$ and $\alpha_0^2$ where the vertical line $\beta = \beta_0$ intercepts the ellipse (details not given). This justifies that the joint-CI (ellipse) and the CB (hyperbola) are mathematically identical.

## 4. The errors-in-variables regressions under homoscedasticity

### *4.1. The estimators of the errors-in-variables regressions*

This section presents the formulas of the regression estimators of model (9) with homoscedastic errors. Four methodologies previously published in the literature are considered: DR (Deming Regression), GR (Galea-Rojas et al. procedure), BLS (Bivariate Least Square regression) and Mandel procedure. The formulas are written with the notations presented in Section 2. Under homoscedasticity, these four methodologies provide identical estimations of the regression line: $\hat{\theta}_{DR} = \hat{\theta}_{GR} = \hat{\theta}_{BLS} = \hat{\theta}_{Mandel}$. However, their covariance matrix are different and lead to different CI. Note that $\sigma_\tau^2$ and $\sigma_\nu^2$ (in the formulas below) can be replaced, if needed, by $S_\tau^2$ and $S_\nu^2$ respectively.

### 4.1.1. *The Deming Regression (DR) estimators*

To take into account the best the errors in both axes, the measurement errors variances ratio must be first defined:

$$\lambda_{XY} = \frac{\sigma_\nu^2/n_Y}{\sigma_\tau^2/n_X} \tag{19}$$

$\lambda_{XY}$ is the ratio of the errors variance in the Y-axis and the errors variance in the X-axis. Usually, the problem of replicated data is not discussed in details in the literature and a 'precision ratio' $\lambda$ is defined by $\lambda = \sigma_\nu^2/\sigma_\tau^2$ (Tan and Iglewicz, 1999) (or inversely Linnet (1990, 1993, 1998, 1999)).
The DR (Deming Regression) is the ML (Maximum Likelihood) solution of model (9) under homoscedasticity and $\lambda_{XY}$ known (Fuller, 1987). In practice, if $\lambda_{XY}$ is unknown, it can be estimated with replicated data. The estimator of $\lambda$ is then given by $\hat{\lambda} = S_\nu^2/S_\tau^2$ (and $\lambda_{XY}$ by $\hat{\lambda}_{XY}$).
The DR minimizes criterion $C_{DR}$ which is the sum of (weighted) squared oblique distances between each point and the line (Linnet, 1999; Tan and Iglewicz, 1999) as shown in Figure 1, the angle of the direction is related to $\lambda_{XY}$ and given by $-\lambda_{XY}/\hat{\beta}$ (Tan and Iglewicz, 1999):

$$C_{DR} = \sum_{i=1}^{N}\left(\lambda_{XY}\left(X_i - \frac{Y_i + \lambda_{XY}X_i/\hat{\beta} - \hat{\alpha}}{\hat{\beta} + \lambda_{XY}/\hat{\beta}}\right)^2 + \left(Y_i - \hat{\alpha} - \frac{\hat{\beta}Y_i + \lambda_{XY}X_i - \hat{\alpha}\hat{\beta}}{\hat{\beta} + \lambda_{XY}/\hat{\beta}}\right)^2\right)$$

The DR estimators are given by:

$$\hat{\beta}_{DR} = \frac{S_{yy} - \lambda_{XY}S_{xx} + \sqrt{(S_{yy} - \lambda_{XY}S_{xx})^2 + 4\lambda_{XY}S_{xy}^2}}{2S_{xy}} \text{ and } \hat{\alpha}_{DR} = \overline{Y} - \hat{\beta}_{DR}\overline{X} \tag{20}$$

The assumption of DR is the constancy of $\lambda_{XY}$. This assumption is fulfilled with homoscedasticity and balanced design (i. e., $n_{X_i}$ and $n_{Y_i}$ constant).

### 4.1.2. *The Galea-Rojas et al. procedure*

Galea-Rojas et al. (2003) propose a regression model based on a paper previously published by Ripley and Thompson (1987) where maximum likelihood is applied to take into account the errors and heteroscedasticity in both axes. The formulas are, here, given under homoscedasticity and with replicated data. The estimators of the parameters are:

$$\hat{\beta}_{GR} = \frac{\sum_{i=1}^{N} W_{GR}\hat{x}_i(Y_i - \overline{Y})}{\sum_{i=1}^{N} W_{GR}\hat{x}_i(X_i - \overline{X})} = \frac{\sum_{i=1}^{N} \hat{x}_i(Y_i - \overline{Y})}{\sum_{i=1}^{N} \hat{x}_i(X_i - \overline{X})} \text{ and } \hat{\alpha}_{GR} = \overline{Y} - \hat{\beta}_{GR}\overline{X} \tag{21}$$

where

$$W_{GR} = \frac{1}{\frac{\sigma_\nu^2}{n_Y} + \hat{\beta}_{GR}^2\frac{\sigma_\tau^2}{n_X}} \text{ and } \hat{x}_i = \frac{\frac{\sigma_\nu^2}{n_Y}X_i + \hat{\beta}_{GR}\frac{\sigma_\tau^2}{n_X}(Y_i - \hat{\alpha}_{GR})}{\frac{\sigma_\nu^2}{n_Y} + \hat{\beta}_{GR}^2\frac{\sigma_\tau^2}{n_X}}$$

$\hat{x}_i$ is the abscissa of the projection of the $i^{th}$ point to the line in the oblique direction defined in the previous section.

#### 4.1.3. *The Bivariate Least Square regression: BLS*

The Bivariate Least Square regression, BLS, is a generic name but this article refers to the papers published first by Lisý et al. (1990) and later by other authors (Martínez et al., 1999, 2002; del Río et al., 2001; Riu and Rius, 1996). BLS can take into account error and heteroscedasticity in both axes and is written usually in matrix notation (Lisý et al., 1990; Martínez et al., 1999, 2002; del Río et al., 2001; Riu and Rius, 1996). Its formulas are given, here, under homoscedasticity and with replicated data. The BLS minimizes the criterion $C_{BLS}$:

$$C_{BLS} = \frac{1}{W_{BLS}} \sum_{i=1}^{N} (Y_i - \hat{\alpha} - \hat{\beta} X_i)^2 = (N-2)s^2_{BLS} \text{ with } W_{BLS} = \sigma^2_{\varepsilon} = \frac{\sigma^2_{\nu}}{n_Y} + \hat{\beta}^2 \frac{\sigma^2_{\tau}}{n_X}$$

Practically, the estimations of the parameters (the $b$ vector) are computed by iterations with the following formula:

$$Rb = g \tag{22}$$

where

$$R = \frac{1}{W_{BLS}} \begin{pmatrix} N & \sum_{i=1}^{N} X_i \\ \sum_{i=1}^{N} X_i & \sum_{i=1}^{N} X_i^2 \end{pmatrix}, \; b = \begin{pmatrix} \hat{\alpha}_{BLS} \\ \hat{\beta}_{BLS} \end{pmatrix},$$

and

$$g = \frac{1}{W_{BLS}} \begin{pmatrix} \sum_{i=1}^{N} Y_i \\ \sum_{i=1}^{N} \left( X_i Y_i + \hat{\beta}_{BLS} \frac{\sigma^2_{\tau}}{n_X} \frac{(Y_i - \hat{\alpha}_{BLS} - \hat{\beta}_{BLS} X_i)^2}{W_{BLS}} \right) \end{pmatrix}$$

Even if the parameters $\sigma^2_{\tau}$ and $\sigma^2_{\nu}$ are present separately in the formula, the solution $b$ only depends of the ratio $\lambda_{XY}$.

#### 4.1.4. *The Mandel procedure*

Mandel developed a regression in the context of inter-laboratories studies (Mandel, 1984) that can take into account the correlation between the error terms (as he regressed the results of a given laboratory with respect to the averages of the results of all laboratories). Since the errors $\tau_{ij}$ and $\nu_{ij}$ are, here, uncorrelated, it can be shown that Mandel's regression is exactly equivalent to DR (if the correlation term is set to zero). The Mandel's procedure consists in transforming the $(X,Y)$ data into $(U = X_i + kY_i, V = Y_i - \hat{\beta}_{Mandel} X_i)$ data such that $U$ has a very small error. The OLS's regression is then applied to the $(U,V)$ data and transformed back into the $(X,Y)$ space to finally get a regression line which takes into account errors in both axes (and their correlation). By using $\lambda_{XY}$ instead of $\lambda$ in the Mandel's procedure (with uncorrelated errors), the formulas are:

$$\hat{\beta}_{Mandel} = \frac{S_{xy} + kS_{yy}}{S_{xx} + kS_{xy}} \text{ and } \hat{\alpha}_{Mandel} = \overline{Y} - \hat{\beta}_{Mandel} \overline{X} \text{ with } k = \frac{\hat{\beta}_{Mandel}}{\lambda_{XY}} \tag{23}$$

$\hat{\beta}_{Mandel}$ can be computed by iterations or by solving a $2^{nd}$ degree equation. By analogy, the following notations will also be used:

$$\overline{U} = \frac{1}{N} \sum_{i=1}^{N} U_i \text{ and } \overline{V} = \frac{1}{N} \sum_{i=1}^{N} V_i,$$

$$S_{uu} = \sum_{i=1}^{N}(U_i - \overline{U})^2,\ S_{vv} = \sum_{i=1}^{N}(V_i - \overline{V})^2 \text{ and } S_{uv} = \sum_{i=1}^{N}(U_i - \overline{U})(V_i - \overline{V}) = 0$$

### 4.2. *The joint-CI and confidence bands of the errors-in-variables regressions*

This section gives the approximate covariance matrix $\hat{\Sigma}$ of the estimates $\hat{\theta} = (\hat{\alpha}, \hat{\beta})'$ of the errors-in-variables regression coefficients $\theta$ presented in section 4.1 in order to compute the joint-CI for $\theta$ or the CB for the regression line (if needed, $\sigma_\tau^2$ and $\sigma_\nu^2$ can be replaced by $S_\tau^2$ and $S_\nu^2$). The joint-CI are all confidence ellipses centered on the same point (as the estimators given in the previous section are identical) but with different shapes and are all approximate. The confidence ellipse for $\theta$ can be computed with the following formula:

$$(\hat{\theta} - \theta)'\hat{\Sigma}^{-1}(\hat{\theta} - \theta) < c \tag{24}$$

where the critical constant $c$ is chosen suitably depending on whether $\chi^2_{1-\gamma,2}$ (the $100(1-\gamma)\%$ percentile of a $\chi^2$ distribution with 2 df) or $2F_{1-\gamma,2,N-2}$ is used as the approximate distribution. This confidence ellipse can be represented equivalently as a CB:

$$x'\theta \in x'\hat{\theta} \pm \sqrt{c}\sqrt{x'\hat{\Sigma}^{-1}x} \tag{25}$$

#### 4.2.1. *The variance-covariance matrix of the estimators provided by DR*

Gillard and Iles (2005, 2006) propose to compute the variance-covariance matrix of the estimators by the method of moments. When $\lambda_{XY}$ is assumed to be known, the variances and covariance of the estimators can be computed with the following formulas (which have been modified to take into account the replicated data):

$$S^2_{\hat{\beta}_{DR}} = \frac{S_{xx}S_{yy} - S^2_{xy}}{N\left(\frac{S_{xy}}{\hat{\beta}_{DR}}\right)^2},\ S^2_{\hat{\alpha}_{DR}} = \overline{X}^2 S^2_{\hat{\beta}_{DR}} + \frac{\hat{\beta}^2_{DR}\sigma^2_\tau/n_X + \sigma^2_\nu/n_Y}{N} \text{ and } S_{\hat{\alpha}\hat{\beta}_{DR}} = -\overline{X}S^2_{\hat{\beta}_{DR}} \tag{26}$$

Based on the asymptotic normal distribution of the parameters $\hat{\beta}_{DR}$ and $\hat{\alpha}_{DR}$ (get by ML), it is proposed in this paper to use a F-distribution with $c = 2F_{1-\gamma,2,N-2}$ to prevent the joint-CI or CB being too narrow for small sample sizes.

#### 4.2.2. *The variance-covariance matrix of the estimators provided by Galea-Rojas et al.*

Galea-Rojas et al. (2003) provide the asymptotic variance-covariance matrix of the parameters derived by ML. Under homoscedasticity and with replicated data, the asymptotic variance-covariance matrix of the parameters is given by:

$$\Sigma_{GR} = W_n^{-1}V_nW_n^{-1}/N, \tag{27}$$

where

$$W_n = \frac{W_{GR}}{N}\begin{pmatrix} N & \sum_{i=1}^N \xi_i \\ \sum_{i=1}^N \xi_i & \sum_{i=1}^N \xi_i^2 \end{pmatrix} \text{ and } V_n = W_n + \begin{pmatrix} 0 & 0 \\ 0 & k_{GR} \end{pmatrix}$$

with

$$k_{GR} = \frac{W_{GR}}{C} \text{ and } C = \frac{1}{\sigma_\tau^2/n_X} + \frac{\beta_{GR}^2}{\sigma_\nu^2/n_Y}$$

In practice, to get a consistent estimator of the variance-covariance matrix, $\beta_{GR}^2$ can be replaced by $\hat{\beta}_{GR}^2$, $\xi_i$ by $\hat{x}_i$ and $\xi_i^2$ by $\hat{\xi}_i^2 - 1/C$ (Galea-Rojas et al., 2003). From the Wald statistic given in the literature (Galea-Rojas et al., 2003), the critical constant is $c = \chi^2_{1-\gamma,2}$. The variances of the parameters can also be computed with the following equivalent formulas (Galea-Rojas et al., 2003):

$$\sigma^2_{\hat{\beta}_{GR}} = \frac{1}{SS_W}\left(1 + \frac{Nk_{GR}}{SS_W}\right), \sigma^2_{\hat{\alpha}_{GR}} = \frac{1}{NW_{GR}} + \overline{\xi}^2 \sigma^2_{\hat{\beta}_{GR}} \text{ and } \sigma_{\hat{\alpha}\hat{\beta}_{GR}} = -\overline{\xi}\sigma^2_{\hat{\beta}_{GR}} \tag{28}$$

with $SS_W = W_{GR}\sum_{i=1}^N(\xi_i - \overline{\xi})^2$ and $\overline{\xi} = \frac{\sum_{i=1}^N \xi_i}{N}$.
In practice, $\sigma^2_{\hat{\beta}_{GR}}$, $\sigma^2_{\hat{\alpha}_{GR}}$ and $\sigma_{\hat{\alpha}\hat{\beta}_{GR}}$ can be estimated by replacing $\overline{\xi}$ by $\overline{X}$, and $SS_W$ by $W_{GR}\sum_{i=1}^N(\hat{x}_i^2 - C^{-1} - 2\hat{x}_i\overline{X} + \overline{X}^2)$.

#### 4.2.3. *The variance-covariance matrix of the estimators provided by BLS*

Riu and Rius (1996) propose the following variance-covariance matrix for the BLS parameters:

$$\hat{\Sigma}_{BLS} = s_{BLS}^2 R^{-1} \tag{29}$$

or equivalently:

$$S^2_{\hat{\beta}_{BLS}} = \frac{W_{BLS} N s_{BLS}^2}{N\sum_{i=1}^N X_i^2 - (\sum_{i=1}^N X_i)^2}, S^2_{\hat{\alpha}_{BLS}} = \frac{W_{BLS} s_{BLS}^2 \sum_{i=1}^N X_i^2}{N\sum_{i=1}^N X_i^2 - (\sum_{i=1}^N X_i)^2} \text{ and } S_{\hat{\alpha}\hat{\beta}_{BLS}} = -\overline{X}S^2_{\hat{\beta}_{BLS}} \tag{30}$$

The critical constant $c$ is given by $2\,F_{1-\gamma,2,N-2}$ (Galea-Rojas et al., 2003). The disadvantages of this approximate ellipse (the theoretical background of this joint-CI is not rigorous) can be found in the literature (Galea-Rojas et al., 2003).

#### 4.2.4. *The variance-covariance matrix of the estimators provided by Mandel*

With the Mandel's procedure, the OLS technique is applied in the $(U,V)$ axes (Mandel, 1984) and the variances of the parameters computed with the formulas given in section 3.2. The variances of the parameters $\hat{\beta}_{Mandel}$ and $\hat{\alpha}_{Mandel}$ are derived by the general formula for the propagation of errors from the reconversion to $(X,Y)$ scales:

$$S^2_{\hat{\beta}_{Mandel}} = \frac{(1 + k\hat{\beta}_{Mandel})^2}{S_{uu}} S^2_{e_{Mandel}} \text{ and } S^2_{\hat{\alpha}_{Mandel}} = \left(\frac{1}{N} + \frac{\overline{X}^2(1 + k\hat{\beta}_{Mandel})^2}{S_{uu}}\right) S^2_{e_{Mandel}} \tag{31}$$

with

$$S^2_{e_{Mandel}} = \frac{S_{vv}}{N-2}$$

The covariance and the joint-CI are not provided by Mandel but the covariance can also be easily computed by the formula for the propagation of errors:

$$S_{\hat{\alpha}\hat{\beta}_{Mandel}} = -\overline{X} S^2_{\hat{\beta}_{Mandel}} \tag{32}$$

It is proposed in this paper to use a F-distribution with $c = 2F_{1-\gamma,2,N-2}$ as the Mandel's procedure is based on the OLS technique.

### 4.3. *Coverage probabilities of the joint confidence intervals or confidence bands*

In order to compare the coverage probabilities of the joint-CI or CB provided by the four methodologies presented in the previous sections, $10^5$ samples were simulated with $N = 10$, 20, 50, with unreplicated data ($n_X = n_Y = 1, \lambda = \lambda_{XY}$ known) and under equivalence ($\alpha = 0, \beta = 1, \eta_i = \xi_i$) for the values of $\lambda_{XY}$ given in Table 1 (with $\sigma^2_\nu$ from 0.1 to 2 and $\sigma^2_\tau$ inversely from 2 to 0.1 providing 13 values of $\lambda$ from 0.05 to 20). Different values of $\eta_i$ were drawn randomly from an Uniform distribution $U(10,20)$ for each simulated sample. The corresponding joint-CI or CB were computed for each simulated sample and the coverage probabilities (at a nominal level = 95%) computed per value of $\lambda_{XY}$. Replicated data were also simulated to allow the estimation of $\sigma^2_\nu$ and $\sigma^2_\tau$: with equal number of replicates ($n_X = n_Y = 2$ and $\lambda = \lambda_{XY}$ or $n_X = n_Y = 4$ and $\lambda = \lambda_{XY}$) and with unequal number of replicates ($n_X = 4, n_Y = 2$ and $\lambda_{XY} = 2\lambda$) in such a way that the values of $\lambda_{XY}$ are identical to those of the unreplicated case. To study in more details the effect of the sample size, simulations were run with $\lambda_{XY} = 0.33, 1, 3$, and $N$ from 10 to 100 (10, 12, 14, 16, 20, 30, 50, 75, 100), with or without replicated data. The coverage probabilities are displayed for $\lambda_{XY}$ known in Figure 3 with respect to $\lambda_{XY}$ (left, on a logarithmic scale) and to $N$ (right) (see the working paper Francq and Govaerts (2012) for the replicated data and estimated $\lambda_{XY}$). When the variances are known, all the coverage probabilities are between 93% and 96% and closer to 95% when $\lambda_{XY} > 1$ for the GR, BLS and Mandel procedures. When $N$ increases, the GR and DR are closer to 95% while the BLS and Mandel procedures provide slightly lower coverage probabilities. When the variances are estimated with replicated data, the coverage probabilities provided by the DR are slightly lower but are the closest to 95%. On the other hand, the coverage probabilities provided by the GR's procedure drop because of the uncertainties on the estimated variances but these coverage probabilities increase with $N$. For instance, when $n_X = n_Y = 2$ with $\lambda_{XY} = 1$, the GR outperforms the BLS with $N > 30$ (approximately). The BLS and Mandel methodologies provide similar coverage probabilities with known or unknown variances. In practice, the accuracy of one measurement method is rarely three times higher than the other such that $\lambda_{XY}$ often lies between around 0.33 and 3. In this interval, the DR and GR are always slightly more suitable with known variances while the DR is always more suitable with unknown variances.

TABLE 1. *Values of $\sigma^2_\nu$ and $\sigma^2_\tau$ for the simulations with $n_X = n_Y = 1$ and the corresponding values of $\lambda$ and $\lambda_{XY}$*

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\sigma^2_\nu$ | 0.1 | 0.175 | 0.25 | 0.375 | 0.5 | 0.625 | 0.75 | 0.875 | 1 | 1.25 | 1.5 | 1.75 | 2 |
| $\sigma^2_\tau$ | 2 | 1.75 | 1.5 | 1.25 | 1 | 0.875 | 0.75 | 0.625 | 0.5 | 0.375 | 0.25 | 0.175 | 0.1 |
| $\lambda = \lambda_{XY}$ | 0.05 | 0.1 | 0.167 | 0.3 | 0.5 | 0.714 | 1 | 1.4 | 2 | 3.333 | 6 | 10 | 20 |

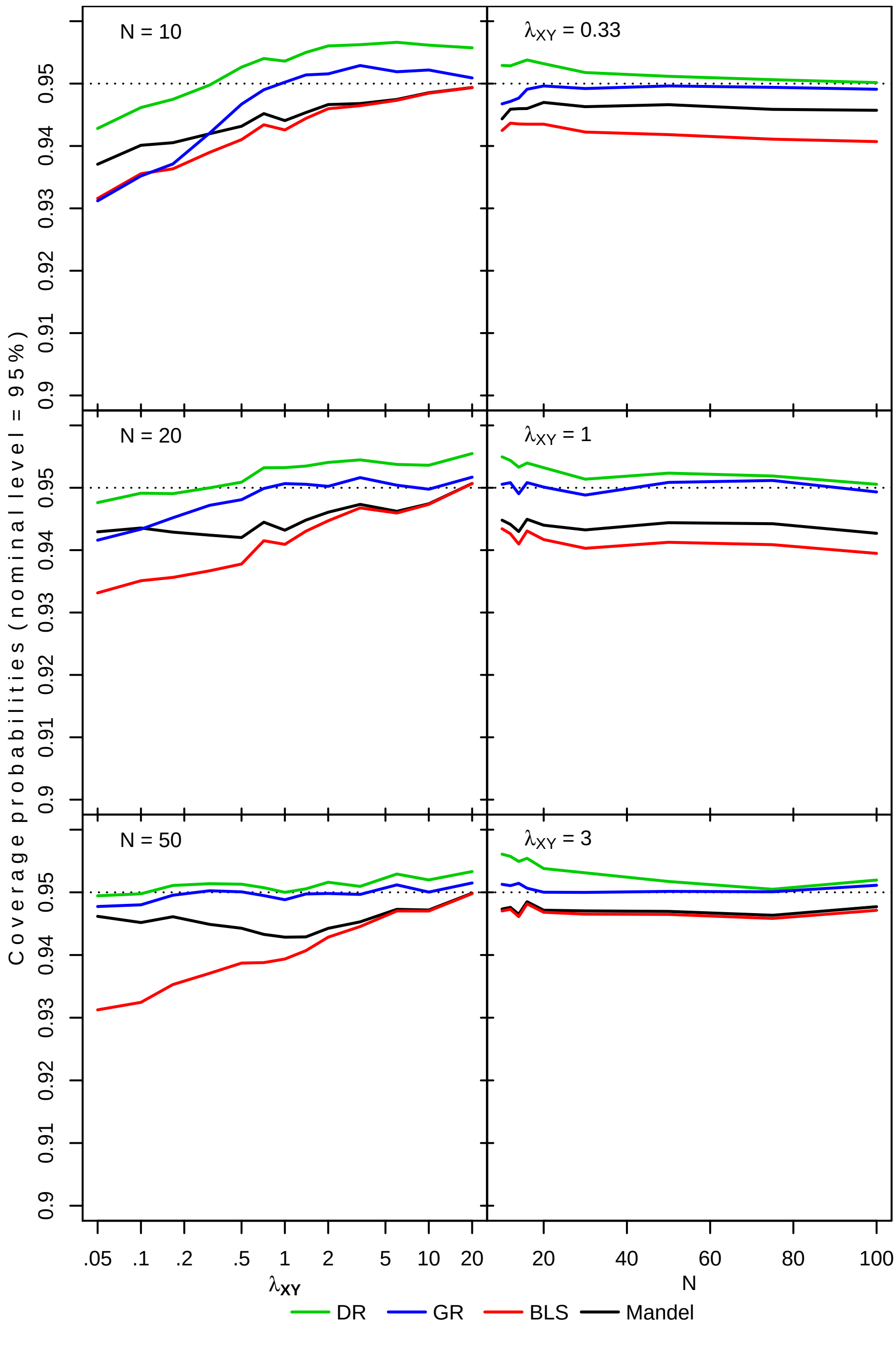


FIGURE 3. *Coverage probabilities of the joint-CI or CB related to $\lambda_{XY}$ in a logarithmic scale with $N = 10$, 20, 50 (left) and related to N for $\lambda_{XY} = 0.33$, 1, 3 (right), $n_X = n_Y = 1$, for the Deming Regression (DR), Galea-Rojas et al. procedure (GR), the Bivariate Least Square regression (BLS) and the Mandel procedure.*

## 5. The errors-in-variables regressions under heteroscedasticity

This section presents the formulas of the regression estimators of model (9) under heteroscedasticity when the variances $\sigma^2_{\tau_i}$ and $\sigma^2_{\nu_i}$ are known or estimated with replicates. The Mandel's regression and the DR are not considered anymore as they are not suitable under heteroscedasticity. The GR procedure and the BLS can take into account the heteroscedasticity and are identical for estimating the regression line ($\hat{\theta}_{GR} = \hat{\theta}_{BLS}$) but the variance-covariance matrix of the parameters are computed differently. The covariance matrix $\hat{\Sigma}$ of the estimates $\hat{\theta} = (\hat{\alpha}, \hat{\beta})'$ given in this section can be plugged in formulas (24) and (25) to get respectively the corresponding joint-CI (confidence ellipse) or CB (with the same critical constant $c$ given in section 4.2).

### 5.1. *The Galea-Rojas et al. procedure*

Based on a paper published previously by Ripley and Thompson (1987), the ML parameters estimators are:

$$\hat{\beta}_{GR} = \frac{\sum_{i=1}^{N} W_{i_{GR}} \hat{x}_i (Y_i - \overline{Y})}{\sum_{i=1}^{N} W_{i_{GR}} \hat{x}_i (X_i - \overline{X})} \text{ and } \hat{\alpha}_{GR} = \overline{Y}_W - \hat{\beta}_{GR} \overline{X}_W, \tag{33}$$

where

$$W_{i_{GR}} = \frac{1}{\frac{\sigma^2_{\nu_i}}{n_{Y_i}} + \hat{\beta}^2_{GR} \frac{\sigma^2_{\tau_i}}{n_{X_i}}} \text{ and } \hat{x}_i = \frac{\frac{\sigma^2_{\nu_i}}{n_{Y_i}} X_i + \hat{\beta}_{GR} \frac{\sigma^2_{\tau_i}}{n_{X_i}} (Y_i - \hat{\alpha}_{GR})}{\frac{\sigma^2_{\nu_i}}{n_{Y_i}} + \hat{\beta}^2_{GR} \frac{\sigma^2_{\tau_i}}{n_{X_i}}},$$

$$\overline{X}_W = \frac{\sum_{i=1}^{N} W_{i_{GR}} X_i}{\sum_{i=1}^{N} W_{i_{GR}}} \text{ and } \overline{Y}_W = \frac{\sum_{i=1}^{N} W_{i_{GR}} Y_i}{\sum_{i=1}^{N} W_{i_{GR}}}$$

The asymptotic variance-covariance matrix of the parameters derived by ML is given by Galea-Rojas et al. (2003):

$$\Sigma_{GR} = W_n^{-1} V_n W_n^{-1} / N, \tag{34}$$

where

$$W_n = \frac{1}{N} \begin{pmatrix} \sum_{i=1}^{N} W_{i_{GR}} & \sum_{i=1}^{N} W_{i_{GR}} \xi_i \\ \sum_{i=1}^{N} W_{i_{GR}} \xi_i & \sum_{i=1}^{N} W_{i_{GR}} \xi_i^2 \end{pmatrix} \text{ and } V_n = W_n + \begin{pmatrix} 0 & 0 \\ 0 & k_{GR} \end{pmatrix}$$

with

$$k_{GR} = \frac{1}{N} \sum_{i=1}^{N} \frac{W_{i_{GR}}}{C_i} \text{ and } C_i = \frac{1}{\sigma^2_{\tau_i}/n_{X_i}} + \frac{\beta^2_{GR}}{\sigma^2_{\nu_i}/n_{Y_i}}$$

In practice, to get a consistent estimator of the variance-covariance matrix, $\beta^2_{GR}$ can be replaced by $\hat{\beta}^2_{GR}$, $\xi_i$ by $\hat{x}_i$ and $\xi_i^2$ by $\hat{\xi}_i^2 - 1/C_i$ (Galea-Rojas et al., 2003). The variances of the parameters can also be computed with the following equivalent formulas (Galea-Rojas et al., 2003):

$$\sigma^2_{\hat{\beta}_{GR}} = \frac{1}{SS_W} \left( 1 + \frac{N k_{GR}}{SS_W} \right), \sigma^2_{\hat{\alpha}_{GR}} = \frac{1}{\sum_{i=1}^{N} W_{i_{GR}}} + \overline{\xi}^2_W \sigma^2_{\hat{\beta}_{GR}} \text{ and } \sigma_{\hat{\alpha}\hat{\beta}_{GR}} = -\overline{\xi}_W \sigma^2_{\hat{\beta}_{GR}} \tag{35}$$

with $SS_W = \sum_{i=1}^{N} W_{i_{GR}} (\xi_i - \overline{\xi}_W)^2$ and $\overline{\xi}_W = \frac{\sum_{i=1}^{N} W_{i_{GR}} \xi_i}{\sum_{i=1}^{N} W_{i_{GR}}}$.

In practice, $\sigma^2_{\hat{\beta}_{GR}}$, $\sigma^2_{\hat{\alpha}_{GR}}$ and $\sigma_{\hat{\alpha}\hat{\beta}_{GR}}$ can be estimated by replacing $\overline{\xi}_W$ by $\overline{X}_W$, and $SS_W$ by $\sum_{i=1}^{N} W_{i_{GR}} (\hat{x}_i^2 - C_i^{-1} - 2\hat{x}_i \overline{X}_W + \overline{X}^2_W)$.

### 5.2. *The Bivariate Least Square regression: BLS*

The BLS regression line minimizes the criterion $C_{BLS}$ (Martínez et al., 2002; del Río et al., 2001; Riu and Rius, 1996):

$$C_{BLS} = \sum_{i=1}^{N} \frac{1}{W_{i_{BLS}}}(Y_i - \hat{\alpha} - \hat{\beta}X_i)^2 = (N-2)s^2_{BLS} \text{ with } W_{i_{BLS}} = \sigma^2_{\varepsilon_i} = \frac{\sigma^2_{\nu_i}}{n_{Y_i}} + \hat{\beta}^2 \frac{\sigma^2_{\tau_i}}{n_{X_i}}$$

The estimations of the parameters are computed by iterations with the following formula:

$$\begin{pmatrix} \sum_{i=1}^{N} \frac{1}{W_{i_{BLS}}} & \sum_{i=1}^{N} \frac{X_i}{W_{i_{BLS}}} \\ \sum_{i=1}^{N} \frac{X_i}{W_{i_{BLS}}} & \sum_{i=1}^{N} \frac{X_i^2}{W_{i_{BLS}}} \end{pmatrix} \begin{pmatrix} \hat{\alpha}_{BLS} \\ \hat{\beta}_{BLS} \end{pmatrix} = \begin{pmatrix} \sum_{i=1}^{N} \frac{Y_i}{W_{i_{BLS}}} \\ \sum_{i=1}^{N} \left( \frac{X_iY_i}{W_{i_{BLS}}} + \hat{\beta}_{BLS} \frac{\sigma^2_{\tau_i}}{n_{X_i}} \frac{(Y_i - \hat{\alpha}_{BLS} - \hat{\beta}_{BLS}X_i)^2}{W^2_{i_{BLS}}} \right) \end{pmatrix} \tag{36}$$

The variance-covariance matrix of the parameters provided by Riu and Rius (1996) is given by:

$$\hat{\Sigma}_{BLS} = s^2_{BLS} R^{-1} \tag{37}$$

or can be computed with the following formulas:

$$S^2_{\hat{\beta}_{BLS}} = \frac{s^2_{BLS} \sum_{i=1}^{N} \frac{1}{W_{i_{BLS}}}}{D_{BLS}}, \; S^2_{\hat{\alpha}_{BLS}} = \frac{s^2_{BLS} \sum_{i=1}^{N} \frac{X_i^2}{W_{i_{BLS}}}}{D_{BLS}} \text{ and } S_{\hat{\alpha}\hat{\beta}_{BLS}} = \frac{s^2_{BLS} \sum_{i=1}^{N} \frac{X_i}{W_{i_{BLS}}}}{D_{BLS}} \tag{38}$$

with $D_{BLS} = \sum_{i=1}^{N} \frac{1}{W_{i_{BLS}}} \sum_{i=1}^{N} \frac{X_i^2}{W_{i_{BLS}}} - \left( \sum_{i=1}^{N} \frac{X_i}{W_{i_{BLS}}} \right)^2$.

### 5.3. *Coverage probabilities of the joint confidence intervals or confidence bands*

The coverage probabilities of the joint-CI provided by GR and BLS are compared in the literature with known variances (Galea-Rojas et al., 2003). Since in practice, the variances are never known but always estimated, this section investigates in more details the coverage probabilities with known and unknown variances: $10^4$ samples were simulated with $N = 10, 12, 15, 20, 30, 50, 75, 100$, with replicated data ($n_X = n_Y = 5$) under equivalence ($\alpha = 0, \beta = 1, \eta_i = \xi_i$). The values of $\xi_i$ were drawn randomly from an Uniform distribution $U(10,20)$ for each simulated sample and the coverage probabilities computed at a nominal level = 95%. The variances are set according to the following functions:

$$\sigma^2_{\tau_i} = 0.45\xi_i - 4 \text{ and } \sigma^2_{\nu_i} = 0.45\xi_i - 4,$$

where the variances $\sigma^2_{\tau_i}$ and $\sigma^2_{\nu_i}$ increase with $\xi_i$ and are equal for a given $\xi_i$ (it is common in practice that the precision of a measurement method decreases when $\xi_i$ increases) and such that $\sigma^2_{\tau_i} = \sigma^2_{\nu_i} = 0.5$ when $\xi_i = 10$ and $\sigma^2_{\tau_i} = \sigma^2_{\nu_i} = 5$ when $\xi_i = 20$. Secondly the variances were chosen independently and randomly ('random heteroscedasticity') from an Uniform distribution $U(0.5,5)$. To study in more details the effect of the replicates when the variances are estimated, simulations were also launched with $N = 20$ and $n_X = n_Y = 2, 4, 6, 8, 10, 12, 15, 20$.

Figure 4 displays the coverage probabilities, which are close to 95% when the variances are known

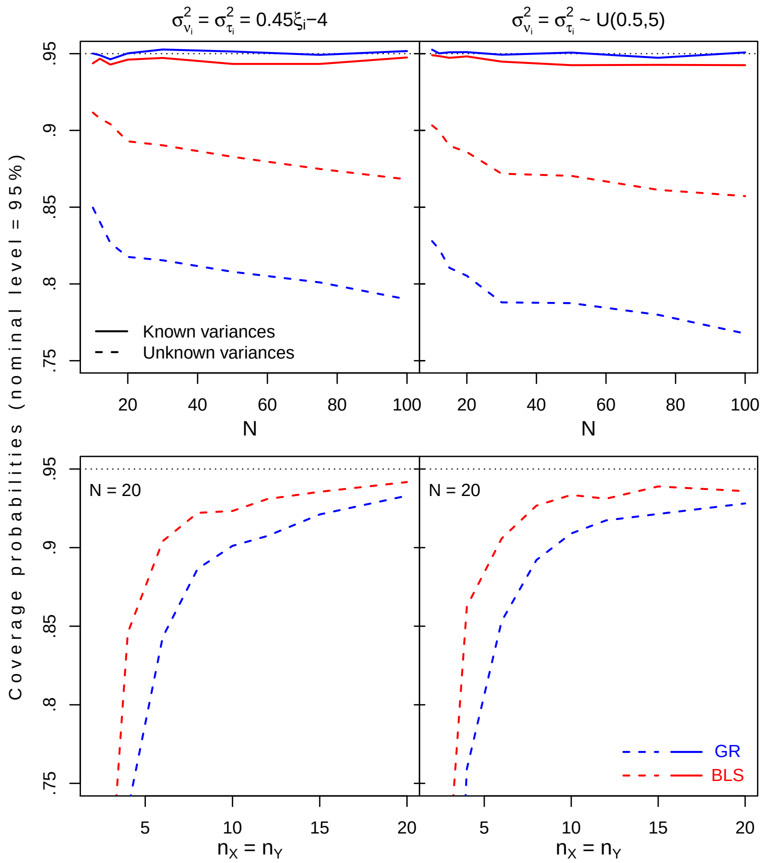


FIGURE 4. *Coverage probabilities of the joint-CI or CB with respect to N (top) or $n_X = n_Y$ (bottom) with heteroscedasticity and known or unknown (and estimated) variances, simulated with a function (left) or randomly (right)*

but closer to 95% for GR. The coverage probabilities collapse drastically when the variances have to be estimated (the number of replicates, $n_X = n_Y = 5$, is too low to estimate a variance) and drop more for GR and especially when N increases or with a random heteroscedasticity. Obviously, when the number of replicates increases, the coverage probabilities increase but BLS still outperforms for $n_X = n_Y = 20$. Actually, the uncertainties on the estimated variances are not taken into account in both methodologies and work is in progress to estimate such regression lines by taking into account additionally the variances uncertainties.

## 6. Applications

Three examples are provided in this section, based on two published data sets, to illustrate the regression techniques and their confidence bands and confidence ellipses. First, the well-known systolic blood pressure data published by Bland and Altman (1999) will be analyzed (replicated data) by assuming the homoscedasticity and secondly under heteroscedasticity. Third, the data set published by Ripley and Thompson (1987) dealing with arsenate ion in water will be analyzed.

### 6.1. The systolic blood pressure data under homoscedasticity

In the systolic blood pressure data (in mmHg), simultaneous measurements were made by each of two observers (denoted J and R) using a sphygmomanometer and by a semi-automatic blood pressure monitor (denoted S). The measurements made by observer R are, here, withdrawn. In other words, the systolic blood pressure was measured three times per patient (85 patients) by the semi-automatic device S and three times per patient by observer J with the manual device. If the mean measures given by S are assigned to the Y-axis and those given by J to the X-axis, it follows that: $N = 85$ $(i = 1,...,85)$, $n_{X_i} = n_X = n_{Y_i} = n_Y = 3\ \forall i$, $\lambda = \lambda_{XY}$.
The variances $\sigma^2_{\tau_i}$ and $\sigma^2_{\nu_i}$ are unknown but can be estimated: $S^2_{\tau_1} = 14.333,\dots,S^2_{\tau_{85}} = 33.333$ and $S^2_{\nu_1} = 9.333,\dots,S^2_{\nu_{85}} = 13$. Moreover, it follows that: $Min(S^2_{\tau_i}) = 1.333, Max(S^2_{\tau_i}) = 197.333$ and $Min(S^2_{\nu_i}) = 1.333, Max(S^2_{\nu_i}) = 1183$.
It is clear that the variances are significantly different from a patient to another one. Nevertheless, as this section assumes homoscedasticity, the 'global' estimates $S^2_\tau$ and $S^2_\nu$ are: $S^2_\tau = 37.408$ and $S^2_\nu = 83.141$, and $\lambda$ $(= \lambda_{XY}$ as $n_X = n_Y)$ is estimated by $\hat{\lambda} = 2.223$.
It follows: $\overline{X} = 127.408, \overline{Y} = 143.027, S_{xx} = 79598.750, S_{yy} = 84916.269, S_{xy} = 67200.826, R^2 = 0.67$
For the different regression's lines, the estimated coefficients are: $\hat{\beta}_{DR} = \hat{\beta}_{GR} = \hat{\beta}_{BLS} = \hat{\beta}_{Mandel} = 0.956$ and $\hat{\alpha}_{DR} = \hat{\alpha}_{GR} = \hat{\alpha}_{BLS} = \hat{\alpha}_{Mandel} = 21.230$.
Figure 5 (left) displays the scatterplot of the data with standard errors of the mean $(S_\tau/\sqrt{n_X}$ and $S_\nu/\sqrt{n_Y})$. Some points are outliers but they will not be removed for didactic purposes. The 95% CB are displayed for the four methodologies (Figure 6-right) and one can see that the equivalence line $(Y = X)$ crosses the CB which means that the manual device and the semi-automatic one are not equivalent: the null hypothesis is rejected; the estimated line is significantly different from the equivalence line. The CB provided by Mandel and BLS are very close to each other (nearly superimposed on the graph) and close to DR away from $\bar{X}$ while the GR is the narrowest. In fact, there are many vertical outliers. When the distance from an outlier to the line increases, $S_{xy}$ increases and the variance-covariance matrix computed by the DR is modified as it is related to $S_{xy}$ in formulas (26). The variance-covariance matrix computed by the BLS is related to the sum of the weighted residuals (30) and obviously this sum increases when a point moves away from the line. On the other hand, the variance-covariance matrix computed by the GR is not related to $S_{xy}$ or the residuals but is related to $W_{GR}$ and $\hat{x}_i$ which are not modified by such outliers. This can also be noticed in Figure 6-left where the equivalence point ($\beta = 1$ and $\alpha = 0$) is outside all the ellipses and the one provided by GR is the smallest. The minor axes of the GR and DR ellipses are equal and by analogy, the widths of their hyperbolic CB are equal at $(\overline{X},\overline{Y})$. The Mandel and BLS ellipses are nearly 9 times larger than the GR ellipse while the DR ellipse is nearly 3 times larger than the GR ellipse.

### 6.2. The systolic blood pressure data under heteroscedasticity

Under heteroscedasticity, the estimated coefficients provided by GR and BLS are: $\hat{\beta}_{GR} = \hat{\beta}_{BLS} = 0.960$ and $\hat{\alpha}_{GR} = \hat{\alpha}_{BLS} = 18.913$. Figure 5 (right) displays the scatterplot of the data with local standard errors of the means. The estimated line is close to the one estimated under homoscedasticity assumption (the parameters are very close to each other). The 95% CB provided by BLS and

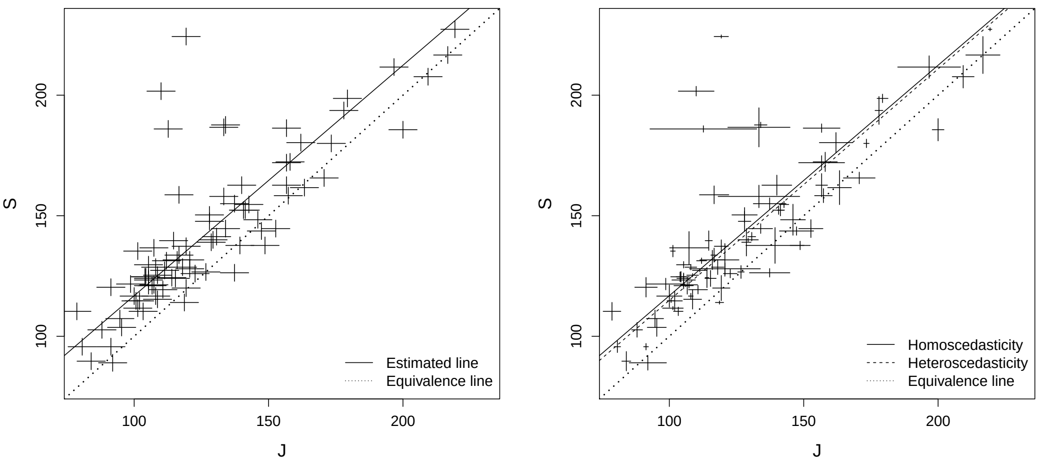


FIGURE 5. *Scatterplot of the systolic blood pressure data under homoscedasticity (left) with the regression line and standard errors of the mean and under heteroscedasticity with local standard errors of the mean (right)*

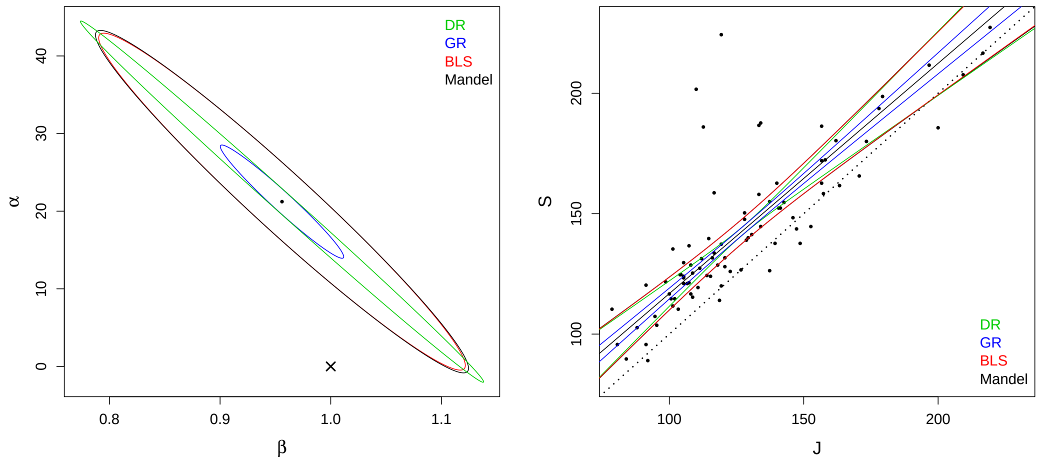


FIGURE 6. *Confidence ellipses (left) and the corresponding confidence bands (right) under homoscedasticity, for the Deming Regression (DR), Galea-Rojas et al. procedure (GR), the Bivariate Least Square regression (BLS) and the Mandel procedure.*

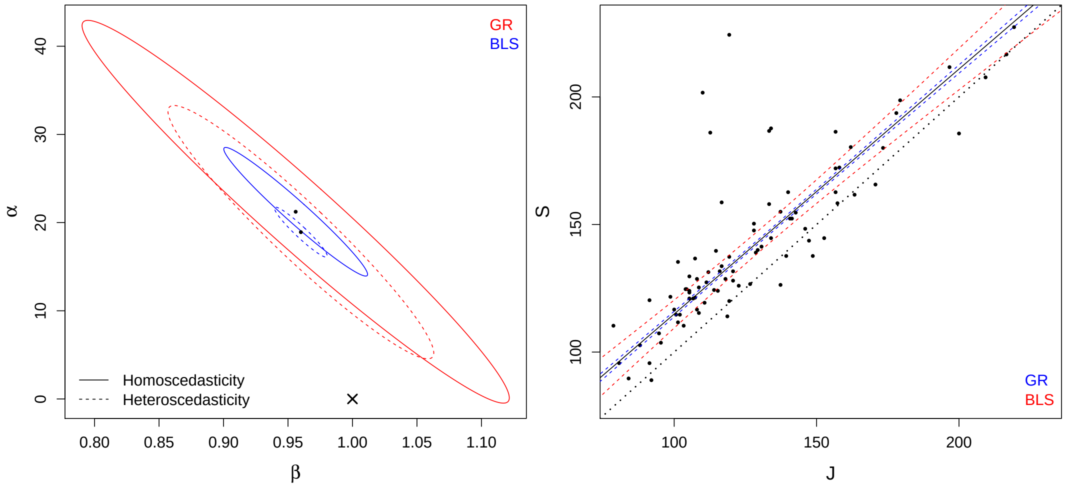


FIGURE 7. *Systolic blood pressure data, confidence ellipses provided by BLS (Bivariate Least Square regression) and GR (Galea-Rojas et al. procedure) with or without heteroscedasticity (left) and the corresponding confidence bands under heteroscedasticity (right)*

GR under heteroscedasticity are displayed in Figure 7-right with the ones under homoscedasticity (for comparison). It can be noticed that the CB are narrower under heteroscedasticity. Actually, some outliers have lower weights under heteroscedasticity which leads to lower variances of the parameters. Like in the previous section, the equivalence line ($Y = X$) is not inside the CB: the equivalence between both devices is rejected. This is confirmed in Figure 7-left where the equivalence point ($\beta = 1$ and $\alpha = 0$) is outside all the ellipses and the ones provided by the GR are the narrowest (under homoscedasticity and heteroscedasticity).

### *6.3. The arsenate ion in natural river water under heteroscedasticity*

In the arsenate ion in natural river water data, 30 pairs of measures are provided by 2 methods: firstly, a continuous selective reduction and atomic absorption spectrometry and secondly, a non-selective reduction, cold trapping and atomic emission spectrometry. The mean measures $(X_i, Y_i)$ with their standard errors of the mean are given and analysed in the literature (Galea-Rojas et al., 2003; Ripley and Thompson, 1987). Figure 8 shows the scatterplot of the data and Figure 9 shows the ellipses of the parameters (left) and the CB (right). Lower concentrations are more frequent than higher concentrations and the errors increase with concentration for both devices (like the simulations in Section 5.3). The estimated line is close to the equivalence line (Figure 8) and this one is inside the hyperbolic CB (Figure 9-right) provided by BLS or GR. Obviously, the equivalence point is inside both ellipses (Figure 9-left). Both CB and both ellipses are, here, very close to each other. This is because there is no vertical outlier in this example. Ideally, the data should be transformed into logarithm but the detailed data are, seemingly, not given in the literature (moreover, these data were analysed in the literature without such transformation Galea-Rojas et al. (2003); Ripley and Thompson (1987)).

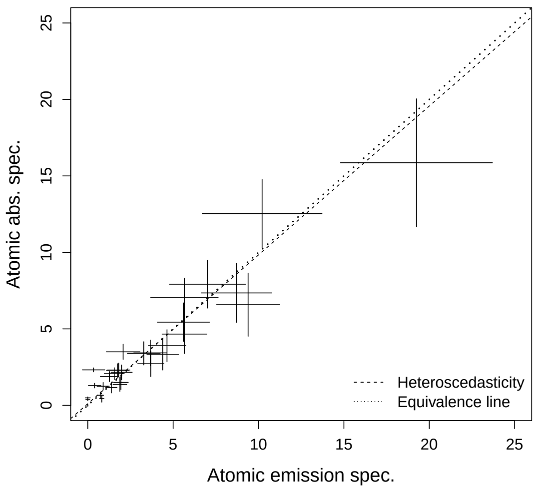


FIGURE 8. *Scatterplot of arsenate ion in natural river water data with the regression line and standard errors of the means*

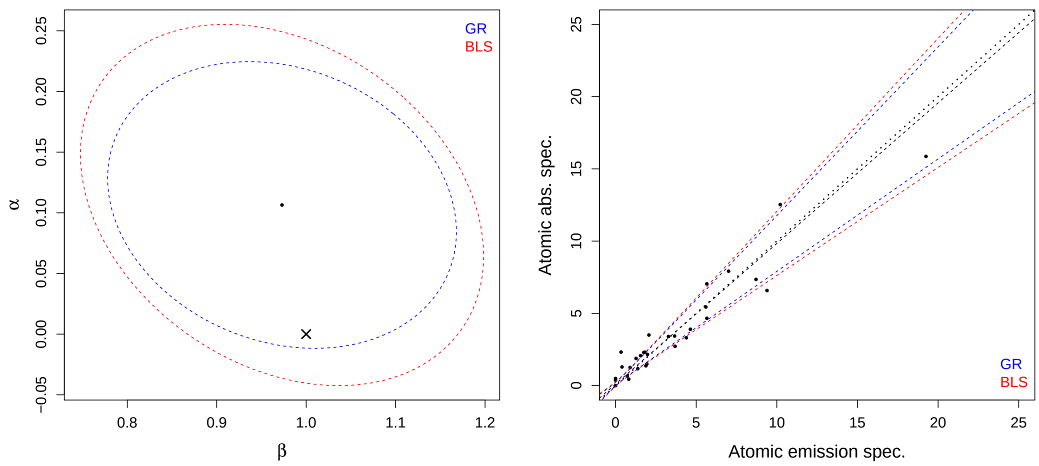


FIGURE 9. *Arsenate ion data, confidence ellipses provided by BLS (Bivariate Least Square regression) and GR (Galea-Rojas et al. procedure) with heteroscedasticity and the corresponding CB*

## 7. Conclusions

Under homoscedasticity, four methodologies (DR, GR, BLS and Mandel) have been compared to estimate a regression line by taking into account errors in both axes. Their confidence ellipse for the parameters estimates can be expressed equivalently by hyperbolic confidence bands for the regression line. These four methodologies give identical estimations of the regression line. However, the variance-covariance matrices of the parameters estimates are computed differently. The confidence ellipses and the CB are therefore dissimilar. The coverage probabilities are close to each other and close to the nominal level when the error variances are known, especially for $\lambda_{XY} > 1$. However, the variance-covariance matrices of the parameters estimates, derived by the method of moments for DR and by the maximum likelihood for the GR, provide slightly better coverage probabilities. Unfortunately, when the error variances are unknown, the coverage probabilities of the GR drop while they are similar for the other procedures. Moreover, the confidence ellipse or CB computed by the GR is the narrowest with vertical outliers, work is still in progress to assess the influence of outliers on the covaraince matrix of the parameters. Under heteroscedasticity, GR and BLS provide the same estimated line. Their coverage probabilities are very close (GR slightly outperforms BLS). However, when the variances are unknown and estimated with replicates, the coverage probabilities of the GR collapse and the BLS outperforms GR. Actually, the uncertainties on the estimated variances are not taken into account and work is still in progress to tackle this problem. To summarize, DR or GR can be recommended under homoscedasticity and BLS or GR under heteroscedasticity by being careful to assess the impact of outliers if needed. Finally, the CB presented in this paper are easier to compute, easier to interpret than an ellipse and can be displayed directly in the $(X,Y)$ space while an ellipse is displayed in a $(\beta,\alpha)$ space.

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