New Measures for (A)Synchrony
With Applications in Infectious Diseases

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Global Outline

- Data
  - HIV serodiscordance among couples in Mozambique
  - Bivariate serology Varicella-Zoster and Parvo B19 virus in Belgium

- Conditional synchrony measure & serodiscordance measure

- Application to HIV serodiscordance

- Alternative new parameterisation

- Application to HIV serodiscordance and VZV-Parvo serology

- Discussion
# HIV serodiscordance among couples in Mozambique

National Survey of Prevalence, Risk Behaviour & Information about HIV & AIDS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Type</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At the individual level</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV status woman/man</td>
<td>binary</td>
<td>0: HIV Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1: HIV Positive</td>
</tr>
<tr>
<td>Union number woman/man</td>
<td>binary</td>
<td>1: once (reference category)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: more than once</td>
</tr>
<tr>
<td>Condom used by woman/man</td>
<td>binary</td>
<td>1: used (reference category)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: not used</td>
</tr>
<tr>
<td>STID woman/man</td>
<td>binary</td>
<td>0: no (in past year)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1: yes (in past year)</td>
</tr>
<tr>
<td><strong>At the level of the couple</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wealth index</td>
<td>trinomial</td>
<td>1: poorer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: middle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3: richer (reference category)</td>
</tr>
<tr>
<td><strong>At the level of the province</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV prevalence of province</td>
<td>trinomial</td>
<td>1: &lt; 5% (reference category)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2: 5% – 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3: &gt; 15%</td>
</tr>
</tbody>
</table>
Bivariate serology VZV and Parvo B19 in Belgium

Top left: proportion tested positive on both
Lower left: positive on VZV only

Top right: positive on Parvo B19 only
Lower right: negative on both
Conditional synchrony measure & serodiscordance measure

Parameterizations bivariate binary data

\[ \pi_{j_1 j_2} = P(y_1 = j_1, y_2 = j_2), \quad j_1, j_2 = 0, 1. \]

\[
\begin{array}{c|cc}
  & 0 & 1 \\
\hline
0 & \pi_{00} & \pi_{01} \\
1 & \pi_{10} & \pi_{11} \\
\hline
\pi_{+0} & \pi_{+1} & 1
\end{array}
\]

3 non-redundant parameters

- any 3 out of \{\pi_{00}, \pi_{01}, \pi_{10}, \pi_{11}\}
- bivariate Dale model
  - marginal success probabilities \(\pi_{1+}, \pi_{+1}\)
  - odds ratio \(\frac{\pi_{00}\pi_{11}}{\pi_{10}\pi_{01}}\)
- marginal probabilities combined with other association parameters
Conditional synchrony measure & serodiscordance measure

Odds ratio dominated by 0-0 cases

HIV status of woman $y_1$ and man $y_2$: OR=$14.8$

<table>
<thead>
<tr>
<th></th>
<th>$y_2$</th>
<th>0</th>
<th>1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$y_1$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1852</td>
<td>130</td>
<td>1982</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>124</td>
<td>129</td>
<td>253</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1976</td>
<td>259</td>
<td>2235</td>
<td></td>
</tr>
</tbody>
</table>
Conditional synchrony measure & serodiscordance measure

Marginal success probabilities $\pi_{1+}, \pi_{+1}$ combined with

- conditional symmetry measure (CSM, Faes et al., JASA, 2008)

$$\text{CSM} = \frac{\pi_{11}}{\pi_{10} + \pi_{01} + \pi_{11}}$$

or

- conditional discordance measure (Juga et al., PLoS ONE, 2017)

$$\text{CDM} = \frac{\pi_{10} + \pi_{01}}{\pi_{10} + \pi_{01} + \pi_{11}}$$
Application to HIV serodiscordance

HIV status
- of a couple $j = 1, \ldots, n_i$
- in enumeration area $i = 1, \ldots, N$

Three logit models for three probabilities

$$\text{logit}(\pi_{1+},ij) = \beta_1^T x_{1,ij} + b_{F,i}$$
$$\text{logit}(\pi_{+1},ij) = \beta_2^T x_{2,ij} + b_{M,i}$$
$$\text{logit}(\text{CDM}_{ij}) = \beta_3^T x_{3,ij} + b_{D,i}$$

where

$$(b_{F,i}, b_{M,i}, b_{D,i}) \sim N_3(0, V_{RV})$$
Application to HIV serodiscordance

Final model: $b_{F,i} = b_{M,i}$, no $b_{D,i}$, partly common effects, AIC=2571.8

<table>
<thead>
<tr>
<th>Effect</th>
<th>HIV Woman Estimates(SE)</th>
<th>HIV Man Estimates(SE)</th>
<th>CDM Estimates(SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-3.53(0.254)*</td>
<td>1.67(0.440)*</td>
<td></td>
</tr>
<tr>
<td>HIV prevalence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$5 - 15%$</td>
<td>1.10(0.248)*</td>
<td>-0.56(0.452)</td>
<td></td>
</tr>
<tr>
<td>$&gt; 15%$</td>
<td>1.93(0.264)*</td>
<td>-1.08(0.455)*</td>
<td></td>
</tr>
<tr>
<td>Union number woman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than once</td>
<td>0.79(0.189)*</td>
<td>0.44(0.165)*</td>
<td>-0.57(0.232)*</td>
</tr>
<tr>
<td>Union number man</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than once</td>
<td>0.11(0.150)</td>
<td>0.37(0.144)*</td>
<td>-</td>
</tr>
<tr>
<td>Condom use man</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not used</td>
<td>0.64(0.251)*</td>
<td>0.03(0.248)</td>
<td>-</td>
</tr>
<tr>
<td>Wealth index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorer</td>
<td>-0.62(0.172)*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>-0.39(0.177)*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Variance component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>0.46(0.115)†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Significant at 5% level
† Significant at 5% level, using $\chi^2_{0,1}$-mixture
Alternative parameterisation

Given $\pi_{1+}, \pi_{+1}$ and CDM, the joint distribution $\pi_{j_1j_2}$ is determined as

\[
\pi_{11} = \frac{1 - \text{CDM}}{2 - \text{CDM}} (\pi_{1+} + \pi_{+1})
\]

\[
\pi_{10} = \pi_{1+} - \pi_{11}
\]

\[
\pi_{01} = \pi_{+1} - \pi_{11}
\]

\[
\pi_{00} = 1 - \pi_{01} - \pi_{10} - \pi_{11}
\]

Fréchet-Hoeffding copula bound for joint & marginal distribution functions

\[
\max(0, F_1(y_1) + F_2(y_2) - 1) \leq F(y_1, y_2) \leq \min(F_1(y_1), F_2(y_2))
\]

implies the condition

\[
\max\left\{ 1 - \frac{\pi_{1+}}{\pi_{+1}}, 1 - \frac{\pi_{+1}}{\pi_{1+}} \right\} \leq \text{CDM} \leq \min\{\pi_{1+} + \pi_{+1}, 1\}
\]
Alternative parameterisation

1. Conditional probability $y_1 = 1$, given both disagree

$$
\pi = P(y_1 = 1 | y_1 \neq y_2) = \frac{\pi_{10}}{\pi_{10} + \pi_{01}} \quad 1 - \pi = \frac{\pi_{01}}{\pi_{10} + \pi_{01}}
$$

2. Conditional probability they (dis)agree, given at least one positive

$$
\delta_+ = P(y_1 \neq y_2 | y_1 + y_2 \geq 1) = \frac{\pi_{10} + \pi_{01}}{\pi_{10} + \pi_{01} + \pi_{11}} \quad \sigma_+ = \frac{\pi_{11}}{\pi_{10} + \pi_{01} + \pi_{11}}
$$

3. Conditional probability they (dis)agree, given at least one negative

$$
\delta_- = P(y_1 \neq y_2 | y_1 + y_2 \geq 1) = \frac{\pi_{10} + \pi_{01}}{\pi_{00} + \pi_{10} + \pi_{01}} \quad \sigma_- = \frac{\pi_{00}}{\pi_{00} + \pi_{10} + \pi_{01}}
$$
Alternative parameterisation

Joint probabilities

\[
\begin{align*}
\pi_{00} &= \frac{\sigma_- (1 - \sigma_+)}{1 - \sigma_- \sigma_+}, \\
\pi_{10} &= \frac{(1 - \sigma_-)(1 - \sigma_+)}{1 - \sigma_- \sigma_+} \pi \\
\pi_{01} &= \frac{(1 - \sigma_-)(1 - \sigma_+)}{1 - \sigma_- \sigma_+} (1 - \pi), \\
\pi_{11} &= \frac{\sigma_+ (1 - \sigma_-)}{1 - \sigma_- \sigma_+}.
\end{align*}
\]

Marginal probabilities

\[
\begin{align*}
\pi_{1+} &= \frac{(1 - \sigma_-)(1 - (1 - \sigma_+)(1 - \pi))}{1 - \sigma_- \sigma_+}, \\
\pi_{+1} &= \frac{(1 - \sigma_-)(1 - (1 - \sigma_+ \pi))}{1 - \sigma_- \sigma_+}.
\end{align*}
\]

Odds ratio

\[
\phi = \left( \frac{\sigma_-}{1 - \sigma_-} \right) \left( \frac{\sigma_+}{1 - \sigma_+} \right) \frac{1}{\pi (1 - \pi)}.
\]
Alternative parameterisation

Some considerations

- Fréchet bounds always satisfied
- orthogonality $\pi \perp \sigma_-, \sigma_+$
- $\pi = 0.5$ implies symmetry $\pi_{ij} = \pi_{ji}$
- $\pi = 0.5$ implies marginal homogeneity $\pi_{1+} = \pi_{+1}$
- odds ratio $\phi$ minimal for $\pi = 0.5$
- odds ratio $\phi$ increases with odds of positive and negative synchrony
Application to HIV serodiscordance

\( \pi = \) given the infection statuses of a couple differ, the probability that the female partner is HIV positive

\( \delta_+ = \) given that at least one of the two partners is positive, the probability that only one is positive (+ serodiscordance)

\( \sigma_- = \) given that at most one of the two partners is positive, the probability that both are negative (- seroconcordance)
Application to HIV serodiscordance

HIV status

- of a couple \( j = 1, \ldots, n_i \)
- in enumeration area \( i = 1, \ldots, N \)

Three logit models for three probabilities

\[
\begin{align*}
\text{logit}(\pi_{ij}) & = \beta_1^T x_{1,ij} + b_{\pi,i} \\
\text{logit}(\delta_{+ij}) & = \beta_2^T x_{2,ij} + b_{\delta+,i} \\
\text{logit}(\sigma_{-ij}) & = \beta_3^T x_{3,ij} + b_{\sigma-,i}
\end{align*}
\]

where \((b_{\pi,i}, b_{\delta+,i}, b_{\sigma-,i}) \sim N_3(0, VRV)\)
Application to HIV serodiscordance

Final model: no $b_{\pi,i}$, and $(b_{\delta+,i}, b_{\sigma-,i})$ correlated, AIC=2509.2 $< 2571.8$

<table>
<thead>
<tr>
<th>Effect</th>
<th>$\pi$ Estimates(SE)</th>
<th>$\delta_+$ Estimates(SE)</th>
<th>$\sigma_-$ Estimates(SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.82(0.40)*</td>
<td>2.48(0.69)*</td>
<td>3.65(0.37)*</td>
</tr>
<tr>
<td>HIV prevalence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 – 15%</td>
<td></td>
<td>-</td>
<td>-0.94(0.53)</td>
</tr>
<tr>
<td>&gt; 15%</td>
<td></td>
<td>-</td>
<td>-1.09(0.56)</td>
</tr>
<tr>
<td>Union number woman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than once</td>
<td>-0.57(0.28)*</td>
<td>-0.74(0.26)*</td>
<td>-0.49(0.17)*</td>
</tr>
<tr>
<td>STDI man</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>-</td>
<td>-1.41(0.42)*</td>
</tr>
<tr>
<td>Condom use woman</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not used</td>
<td>-1.86(0.79)*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wealth index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorer</td>
<td>-</td>
<td>1.13(0.37)*</td>
<td>0.42(0.22)</td>
</tr>
<tr>
<td>Middle</td>
<td>-</td>
<td>0.20(0.37)</td>
<td>0.52(0.24)*</td>
</tr>
<tr>
<td>Variance component</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\sigma_+^2$</td>
<td>-</td>
<td></td>
<td>1.29(0.43)†</td>
</tr>
<tr>
<td>$\sigma_-^2$</td>
<td>-</td>
<td></td>
<td>0.72(0.20)†</td>
</tr>
<tr>
<td>$\rho_{\delta+\sigma-}^2$</td>
<td>-</td>
<td></td>
<td>-0.60(0.24)*</td>
</tr>
</tbody>
</table>

* Significant at 5% level  † Significant at 5% level, using $\chi^2_{0,1}$-mixture
Application to VZV-Parvo serology

\( \pi = \) given the infection statuses differ, the probability that the individual is positive for VZV (black)

\( \sigma_+ = \) given that the individual is positive for at least one, the probability that he is positive for both (blue)

\( \sigma_- = \) given that the individual is positive for at most one, the probability that he is negative for both (green)
Useful alternative parametrisation for bivariate binary data
Applications in modelling (con/dis)cordance, (a)synchrony

Other application: accuracy measures for diagnostic tests
Modification to “exchangeable settings”, e.g. homo-sexual couples
Tolerance intervals and (correlated)-errors-in-variables regressions in method comparison studies. Application with the new R package *BivRegBLS*.

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Sanofi (Montpellier, France)
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### Monoaromatics (% w)

<table>
<thead>
<tr>
<th>Sample</th>
<th>HPLC</th>
<th>GC-MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD Guando</td>
<td>18,21</td>
<td>18,24</td>
</tr>
<tr>
<td>LGO Guando</td>
<td>15,41</td>
<td>16,62</td>
</tr>
<tr>
<td>LD Chichimene</td>
<td>19,28</td>
<td>19</td>
</tr>
<tr>
<td>HD Chichimene</td>
<td>17,15</td>
<td>16,96</td>
</tr>
<tr>
<td>LGO Chichimene</td>
<td>13,54</td>
<td>13,74</td>
</tr>
<tr>
<td>LD R. Hermoso</td>
<td>16,1</td>
<td>15,98</td>
</tr>
<tr>
<td>LGO R. Hermoso</td>
<td>10,58</td>
<td>11,48</td>
</tr>
<tr>
<td>LD Castilla</td>
<td>19,14</td>
<td>19,86</td>
</tr>
<tr>
<td>HD Castilla</td>
<td>18,85</td>
<td>18,64</td>
</tr>
<tr>
<td>LGO Castilla</td>
<td>15,5</td>
<td>14,1</td>
</tr>
<tr>
<td>LD Guaduas</td>
<td>23,74</td>
<td>23,63</td>
</tr>
<tr>
<td>HD Guaduas</td>
<td>18,99</td>
<td>18,98</td>
</tr>
<tr>
<td>LD Toqui-Toqui</td>
<td>20,47</td>
<td>20,75</td>
</tr>
<tr>
<td>HD Toqui-Toqui</td>
<td>18,42</td>
<td>17,97</td>
</tr>
<tr>
<td>LGO Toqui Toqui</td>
<td>16,53</td>
<td>16,4</td>
</tr>
</tbody>
</table>

**Ferrer, Celis, Velandia. Development of a methodology to determine the aromatic structural distribution in light and medium petroleum fractions by HPLC. Cienc. Tecnol. Futuro, 2006; 3 (2), 149-162.**

**N = 35 samples, unreplicated data**

**Question:** is HPLC *equivalent* to GC-MS?
The systolic blood pressure data (mmHg)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sphygometer 'J'</th>
<th>Semi automatic 'S'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>J1</td>
<td>J2</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>106</td>
</tr>
<tr>
<td>2</td>
<td>108</td>
<td>110</td>
</tr>
<tr>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>i</td>
<td>(X_i1)</td>
<td>(X_i2)</td>
</tr>
<tr>
<td>…</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>84</td>
<td>106</td>
<td>98</td>
</tr>
<tr>
<td>85</td>
<td>122</td>
<td>112</td>
</tr>
</tbody>
</table>


Question: is J (Manual) equivalent to S (automatic)?
You have to compare 2 measurement methods:

- Can we switch from one to the other without affecting the decision based on the results?
- How to convert results from one to the other?
- Are the measurements given by 2 devices « equivalent »?
- Is there a bias?
- Do they have the same precision?

2 different procedures to deal with method comparison studies:

- *Errors-in-variables models in (X,Y) plot*
- *Bland and Altman approach in (M,D) plot*
Software solution: BivRegBLS R package

https://CRAN.R-project.org/package=BivRegBLS

Tolerance Intervals and Errors-in-Variables Regressions in Method Comparison Studies

→ BLS: Bivariate Least Square regression

Acknowledgement:
BivRegBLS was developed with a partnership between the University of Glasgow and Sanofi

How to use BivRegBLS? Which stat tools to use? A brief tutorial
library(BivRegBLS); data(Aromatics); data(SBP)

res = desc.stat(data = Aromatics, xcol = 3, ycol = 4, Idcol = "Type ")

raw.plot (data.plot = test, xname = "HPLC", yname = "GC MS", graph = "XY.means", col.ID=1:4)
Descriptive statistics and Raw plot - replicated

```r
res = desc.stat (data = SBP, xcol = 2:4, ycol = c("S1", "S2", "S3"))
raw.plot (data.plot = res, xname = "J", yname = "S", graph = "XY.bar.SEM")
raw.plot (data.plot = res, xname = "J", yname = "S", graph = "MD.points")
```

(X,Y) plot

(M,D) plot

Y = X

D = 0

Francq & Berger, BivRegBLS R package
6th IBS CNC
## XY plot versus MD plot

<table>
<thead>
<tr>
<th>XY plot</th>
<th>MD plot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Errors-in-variables regressions</td>
<td>Blant-Altman approach</td>
</tr>
<tr>
<td>Bias?</td>
<td>Differences clinically important?</td>
</tr>
<tr>
<td>Statistical or strict equivalence</td>
<td>Interchangeable?</td>
</tr>
<tr>
<td>$Y_i = \alpha + \beta X_i + \epsilon_i$</td>
<td>Practical or flexible equivalence</td>
</tr>
</tbody>
</table>

- $H_0^\alpha: \alpha = 0$ & $H_0^\beta: \beta = 1$
- Constant bias & Proportional bias

- Ideally, the AI is included inside the acceptance interval

---

**These 2 approaches do not answer the same question!**

**And are not comparable since CI on one hand, and AI (or PI) on the other hand, are two different concepts**
Agreement AI versus Tolerance Intervals TI

- Agreement Interval by Bland-Altman:  
  \[ \overline{D} \pm 1.96 \cdot S_D \]
  - Approximate and does not take into account sampling error
  - Improving the approximation by calculating CIs around each bound is awkward, misleading and confusing

Tolerance Intervals are better than AI:
- easier to calculate, interpret, excellent coverage probabilities and robust!

- beta-expectation tolerance interval (type I, \( \beta \) TI)
  \[ \overline{D} \pm t_{N-1,1-\alpha/2} \cdot S_D \sqrt{1 + \frac{1}{N}} \]
  Ex: We want an interval that contains 95% of the future differences, on average

- beta-gamma tolerance interval (type II, \( \beta\gamma \) TI)
  \[ \overline{D} \pm z_{1-\alpha/2} \cdot S_D \sqrt{1 + \frac{1}{N} \left( \frac{N-1}{\chi_{N-1,\gamma}^2} \right)} \]
  Ex: We want an interval that contains at least 95% of the future differences with 80% confidence level
Cov. Prob. Tolerance Intervals TI – Replicated data

Bland & Altman AI: XL-Al
Francq & Govaerts TI: βγ TI
Horizontal Tolerance Intervals TI – BivRegBLS

res.TI = MD.horiz.lines (data = SBP, xcol = 2:4, ycol = 8:10)

MD.plot (res.TI, accept.int = 10)

AI: [-25.44, 56.68]
βTI: [-6.03, 37.27]
βγTI: [-6.76, 38.00]
95% predictive and 80% confidence levels

Equivalence rejected as the intervals are larger than the acceptance interval [-10,10]

Tolerance intervals are robust to outliers

MD.Plot (res.TI, accept.int = 10, ylim = c(-30,110))
abline (h = -25.44, col = 2); abline (h = 56.68, col = 2)
**MD plot or XY plot?**

**Problem:** what about PI or TI not horizontal? → Regression!

**Similarities between (X,Y) plot and (M,D) plot**

- There is an « analogy » between both approaches
- Tolerance intervals can also be applied with the (X,Y) approach
- The acceptance interval \([-\Delta, \Delta]\) in the Bland & Altman’s approach becomes \(Y = X \pm \Delta\) with the (X,Y) approach

*So, finally, what do we choose? (X,Y) or Bland-Altman (M,D) plot?*
Regressions
Regressions

DR: Deming Regression
BLS: Bivariate Least Square

Ordinary Least Square
Orthogonal Regression
geometric Mean Regression

OLS\textsubscript{v}
OLS\textsubscript{h}

MR + Passing-Bablok (non-para reg)

Francq & Berger, BivRegBLS R package
BLS regression

(X,Y) plot

\[ (X,Y) \text{ plot} \]

\[ \begin{align*}
\lambda_{XY} = \infty \\
\lambda_{XY} = 1 \\
\lambda_{XY} = 0
\end{align*} \]

\[ \begin{align*}
\sigma^2_x = 0 \\
\sigma^2_y = 0
\end{align*} \]

Standardized data

OLSv \quad MR \quad OLSh

\[ W_i \text{ constant} \quad (\text{Homoscedasticity}) \]

Francq & Berger, BivRegBLS R package

6\textsuperscript{th} IBS CNC
Estimator bias (slope under $H_0$)

- No error in X
- No error in Y
Estimator bias (slope under $H_0$)

In $(X,Y)$ plot
DR and BLS are the most suitable regressions whatever $\lambda$ but perform better with $\lambda_{XY} > 1$

In $(M,D)$ plot
all the regressions perform equally at $\lambda_{XY} = 1$ but are biased otherwise
Coverage probabilities (slope under $H_0$)

**Coverage probabilities**

$\lambda_{XY}$ plot:
- Only good when $\lambda_{XY}=1$
- Otherwise the coverages probabilities collapse drastically

$\lambda_{XY}$ plot:
- « good » for BLS and DR

(M,D) plot:
- Only good when $\lambda_{XY}=1$
- Otherwise the coverages probabilities collapse drastically
MD plot: errors-structure

- \((X,Y)\) distribution with a circular pattern centered around the origin.
- \((\text{Aver}, \text{Diff})\) distribution with an elliptical pattern centered around the origin.
- \(\lambda_{(X,Y)}\) correlation between errors.
- Correlation errors table:
  - \((X,Y)\) correlation: 1
  - \((\text{Aver}, \text{Diff})\) correlation: 0, 0.00

Francq & Berger, BivRegBLS R package  6th IBS CNC
The errors terms are **independent** in the (X,Y) approach but **dependent** in the Bland & Altman’s approach (with $\lambda_{BA}=4$).

The more $\lambda$ moves away from 1, the more the correlation between the errors in the (M,D) plot increases!

The only way to estimate a regression line correctly in the (M,D) plot is to take into account this correlation → CBLS regression.
Bias estimator: CBLS

Bernard regression: CBLS
The BLS regression is the most general regression in a XY plot
The CBLS regression is the most general regression in a MD plot

In BivRegBLS, 4 different hyperbolic intervals are available:

res.BLS = BLS (data = SBP, xcol = 2:4, ycol = 8:10, qx = 2, qy = 2)

XY.plot (res.BLS, xname = "J", yname = "S", graph.int = c("CI", "CB", "PI", "GI"))

- **CI**: Confidence Interval (for a mean = prediction without error)
- **CB**: Confidence Bands (for a mean overall = CI for the line)
- **PI**: Prediction Interval (for a single future value)
- **GI**: Generalized prediction Interval (for the mean of q future value)
Confidence and Prediction intervals – CBLS in MD plot

The BLS regression is the most general regression in a XY plot.
The CBLS regression is the most general regression in a MD plot.

res.CBLS = CBLS (data = SBP, xcol = 2:4, ycol = 8:10, qx = 2, qy = 2)
MD.plot (res.CBLS, xname = "J", yname = "S", graph.int = c("CI", "CB", "PI", "GI"), accept.int = 10)
The practical equivalence is rejected for $\Delta = 10$ mmHg.

Francq & Berger, BivRegBLS R package

6th IBS CNC
If there is no replicate:
estimate all the potential solutions between OLS and OLS_h in a XY plot,
or between $\rho_{MD} = -1$ to $+1$ with $\lambda_{MD} = 4$ by the CBLS in a MD plot

```r
res.full = FullCIs.XY(data = Aromatics,
                      xcol = 3, ycol = 4)
GraphFullCIs.XY(res.full,
                graph = "graph.ellipse")
```

**Interpretation:**
The joint hypothesis ($\beta = 1$ & $\alpha = 0$) is rejected whatever the measurement errors.
### BivRegBLS in brief

- 18 functions including 5 graphical functions
- > 200 warnings and error messages to help the user
- > 160 arguments
- > 550 UAT tests
- > 160 UTT tests

<table>
<thead>
<tr>
<th>Main functions</th>
<th>Calculation</th>
<th>Graph</th>
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<td>raw.plot</td>
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<td>CBLS</td>
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<td>Unreplicated data</td>
<td>FullCIs.XY</td>
<td>GraphFullCIs.XY</td>
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<td>FullCIs.MD</td>
<td>GraphFullCIs.MD</td>
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<td>Other</td>
<td>OLSv, OLSh</td>
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<td></td>
<td>DR</td>
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<td></td>
<td>df.WS, anti.log</td>
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</tbody>
</table>

Options not shown:
- Log normal data
- Ratio instead of differences
- Acceptance interval in percentage
- Superimpose a priori estimation to all solutions
- ...
Many reasons to be very confident in results from this package:
a collaboration between University of Glasgow and Sanofi where:

- B.G. Francq brought his **expertise in errors-in-variables regression and R programming**

- Sanofi brought their **expertise in building end-user tools and validating them** (full validation of calculations and use including warning and error messages)

- Sanofi brought a **wide variety of data types and cases** to be handled by the package: CMC, microbiology, early phase I, biomarkers, animal safety, oncology (the project team included statisticians supporting these areas)

Special thanks to the project team
Christophe Agut, Armand Bergès, Bernard Francq, Guy Mathieu, Franck Pellissier, Véronique Onado and Delphine Attonaty for validation support

*Project manager: Marion Berger*
Conclusion

- Tolerance Intervals are better than Agreement Intervals
- BLS (CBLS) is the most general regression in a XY plot (MD plot)
- BLS in XY plot = CBLS in MD plot (coordinate system does not matter)

- You can choose between many intervals according to your objective
- **Easy-to-use**: first glance with 3 arguments only (data=, xcol=, ycol= )
- Give us your feedback

Modeling agreement on a bounded scale

Sophie Vanbelle¹ and Emmanuel Lesaffre²

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² L-Biostat, Catholic University Leuven, Belgium

25 April 2017

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Introduction

Bounded scales
Introduction

Bounded scales

- Scale with beginning and end
Bounded scales

- Scale with beginning and end
- Visual analogous scale (VAS)
Introduction

Bounded scales

- Scale with beginning and end
- Visual analogous scale (VAS)

How happy are you to be here today?

Not happy at all                          Very happy

0                                          10
Bounded scales

- Scale with beginning and end
- Visual analogous scale (VAS)

How happy are you to be here today?
Not happy at all 0 1 2 3 4 5 6 7 8 9 Very happy 10

How happy are you to be here today? (Circle a number)
Not happy at all 0 1 2 3 4 5 6 7 8 9 Very happy 10
Introduction

Bounded scales

- Scale with beginning and end
- Visual analogous scale (VAS)

\[
\begin{array}{c}
\text{How happy are you to be here today?} \\
\text{Not happy at all} & \text{Very happy}
\end{array}
\]

\[
\begin{array}{cccccccccc}
0 & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10
\end{array}
\]

- Percentages
  - % of painful joints in the hands
  - Ejection fraction (%)

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COCO study

Context: hypertension

- is estimated to cause about 12.8% of all death (WHO)
- Modifiable risk factor through life style behavior and medication
- Only 25-50% of controlled blood pressure (poor compliance)
COCO study

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COmpliance and COmplexity of drug regimen in hypertension

- 1260 patients with stable treatment (diuretic drug)
- Evaluation of blood pressure at one regular visit (2005-2006)
- Complexity: number of separate tablets (1, 2, 3)
- Compliance (100mm VAS): patient and physician
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COmpliance and COmplexity of drug regimen in hypertension

- 1260 patients with stable treatment (diuretic drug)
- Evaluation of blood pressure at one regular visit (2005-2006)
- Complexity: number of separate tablets (1, 2, 3)
- Compliance (100mm VAS): patient and physician

Question: agreement(physician, patient) = f(complexity)?
Agreement on quantitative scales

- Two fixed scorers (patient, physician)
- One construct (compliance)
- Closeness between two assessments
- Variation from the 45° line

Concordance correlation coefficient (CCC), (Lin, 1989)

\[
\text{CCC} \in [-1, 1] = \text{function(means, variances, correlation)} = 1 - \text{Expected squared perpendicular deviation from 45° line}
\]
Agreement on quantitative scales

- Two fixed scorers (patient, physician)
- One construct (compliance)
- Closeness between two assessments
- Variation from the $45^\circ$ line

Concordance correlation coefficient (CCC), (Lin, 1989)

$$CCC \in [-1, 1] = \text{function(means,variances,correlation)}$$

$$= 1 - \frac{\text{Expected squared perpendicular deviation from } 45^\circ \text{ line}}{\text{Expected squared perpendicular deviation from } 45^\circ \text{ line}|\text{ind}}$$
Particularity of bounded scales

COCO study

PETRA study

ANTELOPE study

Compliance

Proportion of positive joints

Presence of PE (%)

Density

Density

Density
Particularity of bounded scales

How useful is the CCC, based on the mean and variance?
Dealing with bounded scales

Logit-normal distribution (LN) (Johnson, 1949)

**Principle:** Logit(score) follows a normal distribution

![Logit-Normal Distribution](image)

*Fig. 1. Different LN distributions.*
Bounded coarsened scores (Lesaffre et al., 2007)
Bounded coarsened scores (Lesaffre et al., 2007)

Bounded score = coarsened version of a latent score with LN distribution

33. Indicate on the scale how important is to you for your child to have a ‘healthy mouth’.

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<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

not important at all  | 3.5 | 4.5 | very important

---

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Dealing with bounded scales

Bounded coarsened scores (Lesaffre et al., 2007)

Bounded score = coarsened version of a latent score with LN distribution

Manifest scale

33. Indicate on the scale how important is to you for your child to have a ‘healthy mouth’.

not important at all | very important
0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10

Density

Observed scale: Y=coarsened version of U
Bounded coarsened scores (Lesaffre et al., 2007)

Bounded score = coarsened version of a latent score with LN distribution

33. Indicate on the scale how important is to you for your child to have a ‘healthy mouth’.

Manifest scale → Latent scale (LN)
Bounded coarsened scores (Lesaffre et al., 2007)

Bounded score = coarsened version of a latent score with LN distribution

Manifest scale $\rightarrow$ Latent scale (LN)
Bounded coarsened scores (Lesaffre et al., 2007)

Bounded score = coarsened version of a latent score with LN distribution

Manifest scale

$$\rightarrow$$

Latent scale (LN)

Logit-normal

$$\rightarrow$$

Normal
Particularity of bounded scales

COCO study

PETRA study

ANTELOPE study

Density

Compliance

Proportion of positive joints

Presence of PE (%)
Our strategy

Method

- Generalize the LN to bivariate LN (BLN)
- Coarsened version of a latent score with BLN (volume)
- CCC defined on the normal latent scale
Our strategy

Method

- Generalize the LN to bivariate LN (BLN)
- Coarsened version of a latent score with BLN (volume)
- CCC defined on the normal latent scale

Aim

- means=function(covariates)
- log(variances)=function(covariates), variances>0
- arctnh(CCC)=function(covariates), -1<=CCC<=1
Coarsened scores: likelihood

- Bivariate normal density function $\rightarrow$ BLN $\rightarrow$ compute a volume
- Involves the bivariate normal cumulative density function
Statistical inference

Coarsened scores: likelihood

- Bivariate normal density function $\rightarrow$ BLN $\rightarrow$ compute a volume
- Involves the *bivariate normal cumulative density function*

Problem

- MLE: no analytical solution for bivariate normal CDF
- Approximation by Mee and Owen (1983)
Statistical inference

Coarsened scores: likelihood

- Bivariate normal density function $\rightarrow$ BLN $\rightarrow$ compute a volume
- Involves the bivariate normal cumulative density function

Problem

- MLE: no analytical solution for bivariate normal CDF
- Approximation by Mee and Owen (1983)

Solution

- Bayesian usually shows good frequentist properties
- Flexibility (covariates, missing data)
- Method implemented in standard softwares (JAGS, WinBUGS)
- Vague priors $N(0, 10^{-6})$ for the model parameters
Simulation results (plain=BLN, dashed=classical)

Skewed distribution (J-shape)

Symmetrical distribution (U-shape)
Simulation results (plain=BLN, dashed=classical)

- New approach close to nominal level and outperforms the classical approach
Simulation results (plain=BLN, dashed=classical)

- New approach close to nominal level and outperforms the classical approach
- Classical approach worse for the skewed distribution (use of mean, SD)
Simulation results (plain=BLN, dashed=classical)

- New approach close to nominal level and outperforms the classical approach
- Classical approach worse for the skewed distribution (use of mean, SD)
- Classical approach worse when CCC $\rightarrow$ 1 (based on normal distribution)
COCO study (hypertension): results

Models adjusted for gender, disease duration, tolerability
COCO study (hypertension): results

Models adjusted for gender, disease duration, tolerability

Summary of posterior distributions

---

female, duration=5yrs, tolerability=7

Number of tablets

Mean compliance score

SD(compliance score)

Number of tablets

physician

Patient

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COCO study (hypertension): results

Models adjusted for gender, disease duration, tolerability

Summary of posterior distributions

- Means: No effect of treatment complexity
COCO study (hypertension): results

Models adjusted for gender, disease duration, tolerability

Summary of posterior distributions

- Means: No effect of treatment complexity
- Variances: higher with 1 tablet than 3 tablets (patient)
COCO study (hypertension): results

- Agreement not that high
- → Patient and physician cannot be used interchangeably
COCO study (hypertension): results

- Agreement not that high
- Patient and physician cannot be used interchangeably
- Agreement: higher with 1 and 2 tablets than 3 tablets
COCO study (hypertension): results

- Agreement not that high
- Patient and physician cannot be used interchangeably
- Agreement: higher with 1 and 2 tablets than 3 tablets
- Need of a clear definition of compliance
Discussion

- Vanbelle S. and Lesaffre E., SMMR, DOI: 10.1177/0962280217705709
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