Practical aspects of method comparison studies

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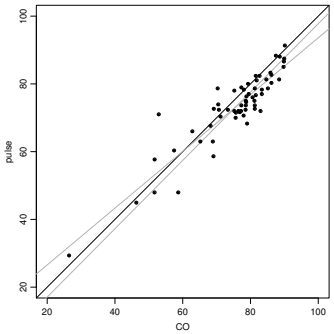
Outline

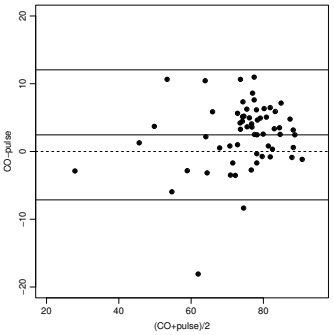
Comparing measurement methods

- Are results systematically different?
- Can one method safely be replaced by another?
- What is the size of measurement errors?
- Different centres use different methods of measurement:
  How do we convert from one method to another?
- How precise is the conversion?

Two methods for oxygen saturation:



Limits of agreement:



Plot differences (D_i) versus averages (A_i).

Limits of agreement:

How large is the difference between a measurement with method 1 and one with method 2 on a (randomly chosen) person?

$$D_i = y_{1i} - y_{2i}, \qquad \bar{D}, \qquad \text{s.d.}(D)$$

"Limits of agreement:"

$$\bar{D} \pm 2 \times \text{s.d.}(D)$$

95% prediction interval for the difference between a pair of future measurements by methods 1 and 2. [1, 2]

Limits of agreement: Model

Methods $m = 1, \ldots, M$, applied to $i = 1, \ldots, I$ individuals:

$$\begin{aligned} y_{mi} &= \alpha_m + \mu_i + e_{mi} \\ &\text{s.d.}(e_{mi}) = \sigma_m \quad \text{— measurement error} \end{aligned}$$

- Two-way analysis of variance model, with unequal variances in columns.
- Different variances are not identifiable without replicate measurements for $M = 2$.

Extension of the model: replicate measurements

$$\begin{aligned} y_{mir} &= \alpha_m + \mu_i + c_{mi} + e_{mir} \\ &\text{s.d.}(c_{mi}) = \tau_m \quad \text{— "matrix"-effect} \\ &\text{s.d.}(e_{mir}) = \sigma_m \quad \text{— measurement error} \end{aligned}$$

- Replicates for each (m, i) is needed to separate τ and σ.
- Even with replicates, the τs are only estimable if $M > 2$.
- Still assumes that the difference between methods is constant.

Extension of the model: non-constant differences

$$y_{mi} = \alpha_m + \beta_m \mu_i + e_{mi}$$

μ_i : "true" individual level

e_{mi} : measurement error, σ_m

- Measurements linearly related to a "true" value, μ_i.
- Not all (α_m, β_m) can be identified.
- The μs are only unique up to a linear transformation.

Relationship between methods

Translation formula from method 1 to method 2 is (for the mean):

$$\begin{aligned} y_2 = \alpha_2 + \beta_2 \mu \;&=\; \alpha_2 + \beta_2(y_1 - \alpha_1)/\beta_1 \\ &=\; \big(\alpha_2 - \alpha_1\beta_2/\beta_1\big) + (\beta_2/\beta_1) y_1 \end{aligned}$$

Intercept and slope going from method 1 to 2:

$$\begin{aligned} \alpha_{2\cdot1} &= \alpha_2 - \alpha_1\beta_2/\beta_1 \\ \beta_{2\cdot1} &= \beta_2/\beta_1 \end{aligned}$$

Invariant under linear transformation of the μs.

Extension with variance components

Three-way layout:
Method, individual, Replicate.
Three two-way interactions:

$$y_{mir} = \alpha_m + \beta_m(\mu_i + a_{ir}) + c_{mi} + d_{mr} + e_{mir}$$

Exchangeability of replicates within methods and individuals determine which interactions are relevant.

Variance components

Method, individual, Replicate.

$$\begin{aligned} y_{mir} &= \alpha_m + \beta_m(\mu_i + a_{ir}) + c_{mi} + d_{mr} + e_{mir} \\ &\quad \text{s.d.}(c_{mi}) = \tau_m \end{aligned}$$

Matrix-effect: Each individual reacts differently to each method.

Only two methods:
τ_1 and τ_2 cannot be separated:

$$\begin{aligned} y_{mir} &= \alpha_m + \beta_m(\mu_i + a_{ir} + c_{mi}) + d_{mr} + e_{mir} \\ &\quad \text{s.d.}(c_{mi}) = \tau \end{aligned}$$

Predicting method 2 from method 1

$$\begin{aligned} y_{10r} &= \alpha_1 + \beta_1(\mu_0 + a_{0r}) + c_{10} + e_{10r} \\ y_{20r} &= \alpha_2 + \beta_2(\mu_0 + a_{0r}) + c_{20} + e_{20r} \\ &\Downarrow \\ y_{20r} &= \alpha_2 + \frac{\beta_2}{\beta_1}(y_{10r} - \alpha_1 - c_{10} - e_{10r}) \\ &\qquad + c_{20} + e_{20r} \end{aligned}$$

The random effects have expectation 0, so:

$$\text{E}(y_{20r}|y_{10r}) = \hat{y}_{20r} = \alpha_2 + \frac{\beta_2}{\beta_1}(y_{k0r} - \alpha_1)$$

$$\text{E}(y_{20r}|y_{10r}) = \hat{y}_{20r} = \alpha_2 + \frac{\beta_2}{\beta_1}(y_{k0r} - \alpha_1)$$

$$\text{var}(\hat{y}_{20r}|y_{10r}) = \left(\frac{\beta_2}{\beta_1}\right)^2(\tau_1^2 + \sigma_1^2) + (\tau_2^2 + \sigma_2^2)$$

The slope is β_2/β_1.
If we do the prediction the other way round we get:

- Same line
- Same limits (they will be $\beta_2 1/\beta_2$ as wide).

Alternating random effects models

Carstensen [3] proposed a ridiculously complicated approach to fit the model

$$y_{mir} = \alpha_m + \beta_m \mu_i + c_{mi} + e_{mir}$$

- For fixed μ it's just a linear mixed model.
- For fixed (α, β) it's just a regression through 0.

— plus a bit of fidgeting with the BLUPs.

Implementation in BUGS

$$y_{mir} = \alpha_m + \beta_m(\mu_i + a_{ir} + c_{mi}) + e_{mir}$$

Non-linear hierarchical model:
Implement in BUGS.

- The model is *symmetrical* in methods.
- Mean is overparametrized.
- Choose a prior (and hence posterior!) for the μs with finite support.
- Keeps the chains nicely in place.

Results from fitting the model

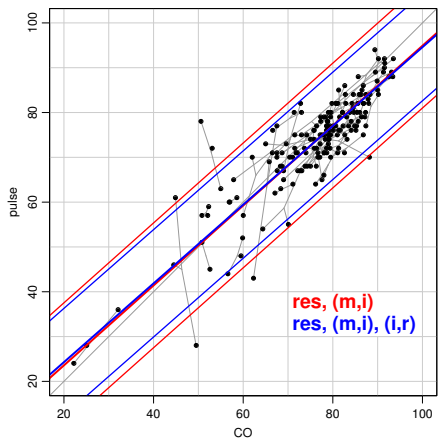
The posterior dist'n of $(\alpha_m, \beta_m, \mu_i)$ is singular.

But the relevant translation quantities are identifiable:

$$\alpha_{2\cdot1} = \alpha_2 - \alpha_1\beta_2/\beta_1$$
$$\beta_{2\cdot1} = \beta_2/\beta_1$$

So are the variance components.

Posterior medians used to devise prediction equations with limits.



$$y_{mir} = \alpha_m + \beta_m(\mu_i + a_{ir} + c_{mi}) + e_{mir}$$

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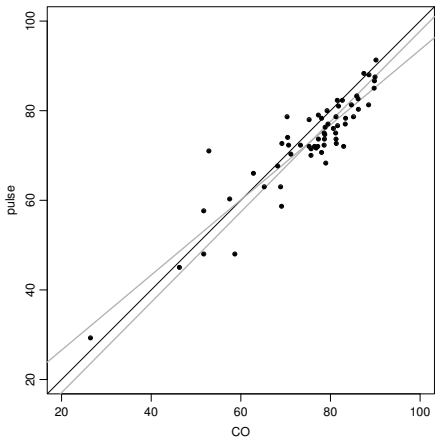

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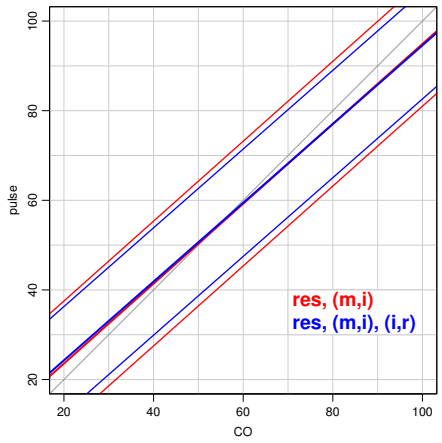

$$y_{mir} = \alpha_m + \beta_m(\mu_i + a_{ir} + c_{mi}) + e_{mir}$$

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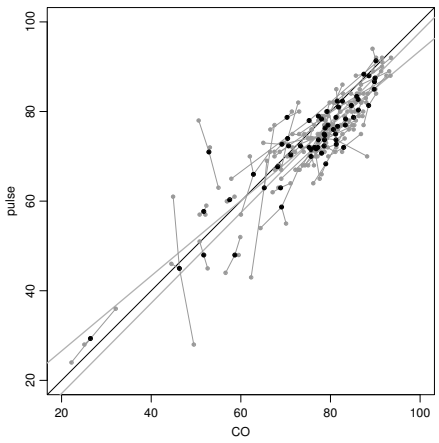

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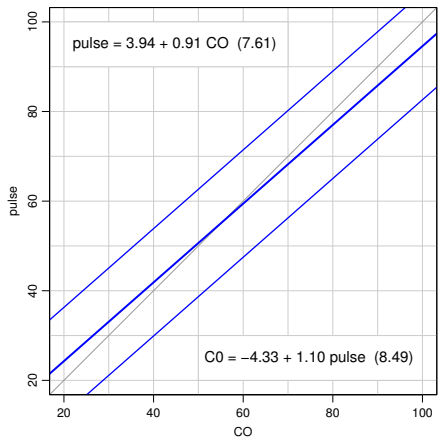

$$y_{mir} = \alpha_m + \beta_m(\mu_i + a_{ir} + c_{mi}) + e_{mir}$$

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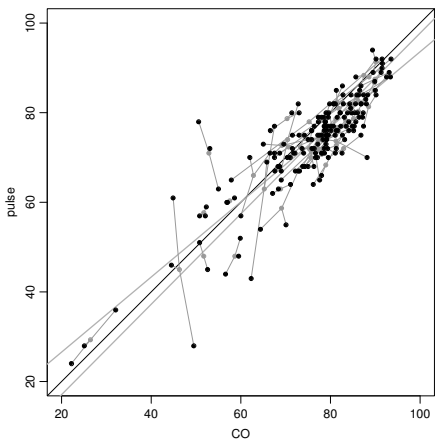

Morale

- Use a proper model for your problem.
- Get the exchangeability right.
- Report the model in a useful way.

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Implemented model:

$$y_{mir} = \alpha_m + \beta_m(\mu_i + a_{ir} + c_{mi}) + e_{mir}$$

- Replicates required.
- R2WinBUGS is required.
- Dataframe with variables meth, item, repl and y.
- The function MethComp writes a BUGS-program, initial values and data to files.
- Runs WinBUGS and sucks results back in to **R**, and gives a nice overview of the conversion equations.

Example output: Oximetry

```
> ox.mi.ir <- MethComp( ox, n.iter=5000 )
> ox.mi.ri

Comparison of 2 methods, using 354 measurements
on 61 individuals, with up to 3 replicate measurements.
( 2 * 61 * 3 = 366 ):

No. individuals with measurements on each method:
       # replicates
Method  1 2  3 Sum
  CO    1 4 56  61
  pulse 1 4 56  61
```


Example output: Oximetry

```
Conversion formulae (y_to = alpha + beta*y_from +/- 2*sd.pred):
    From:    CO                    pulse
         alpha   beta sd.pred     alpha   beta sd.pred
To:
CO       0.000  1.000   4.266    -4.328  1.098   8.487
pulse    3.939  0.911   7.606     0.000  1.000   5.534

Variance components (standard deviations):
                    50%   2.5%   97.5%     0%    100%
sigma.mir[CO]    1.6285 0.2092  2.8274 0.0724  3.4330
sigma.mir[pulse] 4.2580 3.5390  4.9725 3.0670  5.9800
sigma.mi[CO]     4.8043 2.7504 13.3685 2.2597 17.6134
sigma.mi[pulse]  4.3123 2.4981 11.5859 1.9248 13.2186
sigma.ir[CO]     3.9213 3.1452  4.7038 2.7289  5.3129
sigma.ir[pulse]  3.5433 2.7542  4.3516 2.2610  4.8723
```


HbA_{1c} - 3 different instruments

```
> hbv.mi.ir <- MethComp( hbv, n.iter=5000 )
> print( hbv.mi.ir, across=FALSE )

Conversion formula:
 y_to = alpha + beta * y_from +/- 2*sd.pred:
            From:  BR.V2  BR.VC  Tosoh
To:
BR.V2 alpha        0.000 -1.627  1.413
      beta         1.000  1.154  0.946
      sd.pred      0.254  2.079  2.099
BR.VC alpha        1.417  0.000  2.412
      beta         0.867  1.000  0.819
      sd.pred      1.800  0.164  1.927
Tosoh alpha       -1.591 -3.144  0.000
      beta         1.057  1.220  1.000
      sd.pred      2.145  2.249  0.156
```


HbA_{1c} - 3 different instruments

```
Variance components (standard deviations):
                   50%   2.5%  97.5%     0%   100%
sigma.mir[BR.V2] 0.2089 0.1816 0.2401 0.1614 0.2692
sigma.mir[BR.VC] 0.1074 0.0813 0.1286 0.0642 0.1467
sigma.mir[Tosoh] 0.0345 0.0006 0.0824 0.0004 0.0984
sigma.mi[BR.V2]  1.3495 1.0780 1.7742 0.9194 2.1615
sigma.mi[BR.VC]  1.3088 1.0498 1.6979 0.8615 2.1350
sigma.mi[Tosoh]  1.4416 1.0782 5.3653 0.9250 6.3534
sigma.ir[BR.V2]  0.1418 0.1037 0.1882 0.0855 0.2319
sigma.ir[BR.VC]  0.1239 0.0928 0.1572 0.0797 0.1827
sigma.ir[Tosoh]  0.1496 0.1231 0.1815 0.0950 0.2002
```


References

DG Altman and JM Bland.
Measurement in medicine: The analysis of method comparison studies.
The Statistician, 32:307–317, 1983.

JM Bland and DG Altman.
Measuring agreement in method comparison studies.
Statistical Methods in Medical Research, 8:136–160, 1999.

B Carstensen.
Comparing and predicting between several methods of measurement.
Biostatistics, 5(3):399–413, Jul 2004.

MethComp (0.1.0) is available at:
http://www.biostat.ku.dk/~bxc/MethComp
— but not on CRAN yet.