Statistical Analysis of Method Comparison studies

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Tutorial, SISMEC, Ancona, Italy
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http://BendixCarstensen.com/MethComp/Ancona.2011

Comparing two methods with one measurement on each
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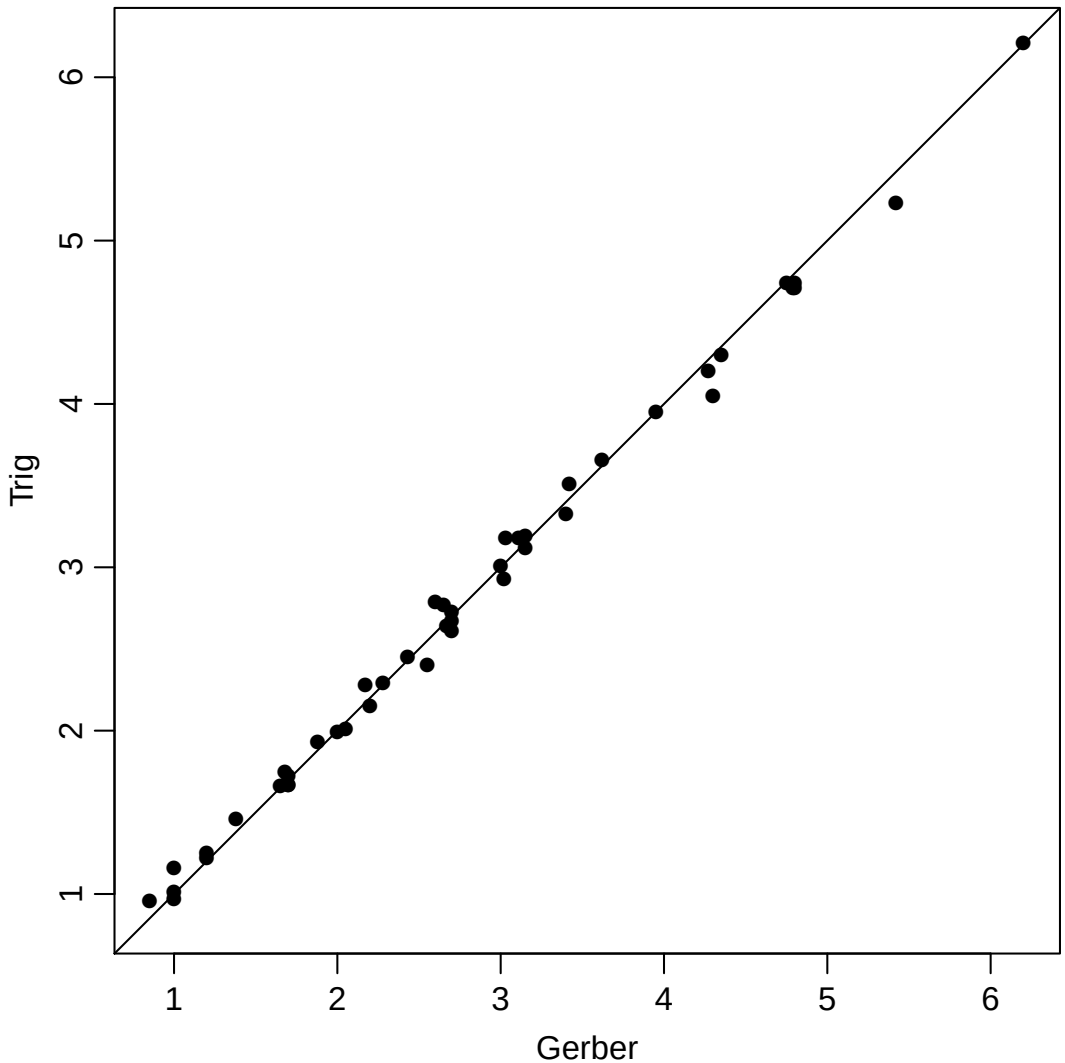
Comparing measurement methods

General questions:

- 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 can we convert from one method to another?
- How precise is the conversion?

Two methods for measuring fat content in human milk:



The relationship looks like:

$$y_1 = a + by_2$$

Two methods — one measurement by each

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

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

"Limits of agreement:"

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

95% prediction interval for the difference between a measurement by method 1 and one by method 2. [1, 2]

Limits of agreement: Interpretation

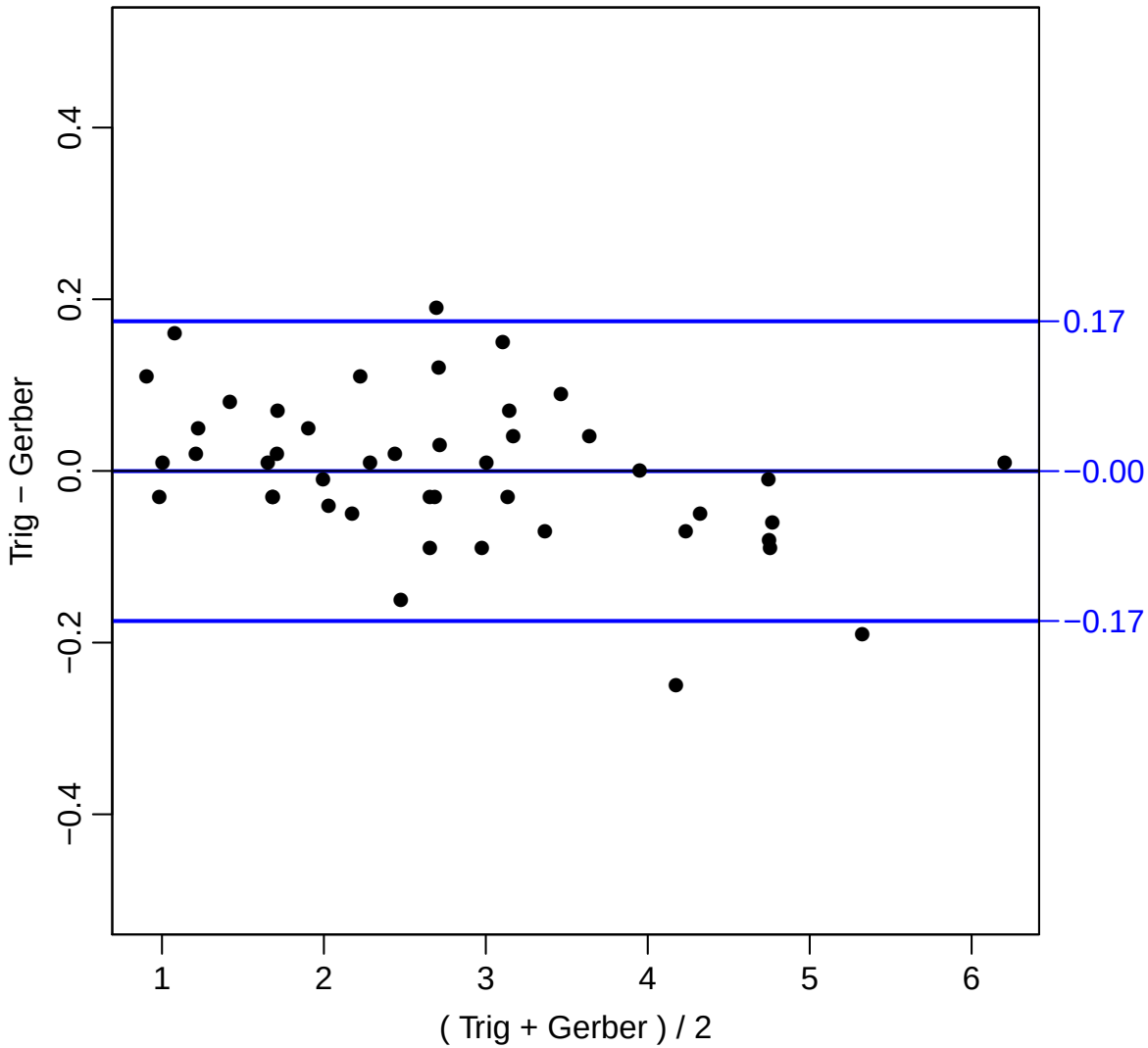
- If a new patient is measured **once** with each of the two methods, the difference between the two values will with 95% probability be within the limits of agreement.
- This is a **prediction** interval for a (future) difference.
- Requires a **clinical** input:
  Are the limits of agreement sufficiently narrow to make the use of either of the methods clinically acceptable?
- Is it relevant to test if the mean is 0?

Limits of agreement: Test?

Testing whether the difference is 0 is a bad idea:

- If the study is sufficiently small this will be accepted even if the difference is important.
- If the study is sufficiently large this will be rejected even if the difference is clinically irrelevant.

Limits of agreement:



Plot differences (D_i) versus averages (A_i).

Model in "Limits of agreement"

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

$$\begin{aligned} y_{mi} &= \alpha_m + \mu_i + e_{mi} \\ e_{mi} &\sim \mathcal{N}(0, \sigma_m^2) \quad \text{measurement error} \end{aligned}$$

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

Limits of agreement:

Usually interpreted as the likely difference between two future measurements, one with each method:

$$\widehat{y_2 - y_1} = \hat{D} = \alpha_2 - \alpha_1 \pm 1.96\,\mathrm{s.d.}(D)$$

Normally we use 2 instead of 1.96.

Neither are formally correct if we take the model seriously:

- Use a t-quantile with $I - 1$ d.f.
- Estimation s.d. of $\alpha_2 - \alpha_1$ is $\sigma/\sqrt{I}$.

So we should use $t_{0.95} \times \sqrt{(I+1)/I}$ instead.
This is 2.08 for $I = 30$ and less than 2 if $I > 85$.

Limits of agreement:

Limits of agreement can be converted to a prediction interval for y_2 given y_1, by solving for y_2:

$$y_2 - y_1 = \alpha_2 - \alpha_1 \pm 2\,\text{s.d.}(D)$$

which gives:

$$\hat{y}_{2|1} = \hat{y}_2 | y_1 = \alpha_2 - \alpha_1 + y_1 \pm 2\,\text{s.d.}(D)$$

Introduction to computing
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Structure of practicals

This tutorial is both theoretical and practical, i.e. the aim is to convey a basic understanding of the problems in method comparison studies, but also to convey practical skills in handling the statistical analysis.

- **R** for data manipulation and graphics.
- So we assume familiarity with **R**.
- Occasionally `BUGS` for estimation in non-linear variance component models.
- `BUGS` is hidden inside an **R**-function.

How it works

Example data sets are included in the `MethComp` package.

Functions in `MethComp` are based on a data frame with a particular structure; a `Meth` object:

`meth` — method (factor)
`item` — item, person, individual, sample (factor)
`repl` — replicate (if present) (factor)
`y` — the actual measurement (numerical)

Once converted to `Meth`, just use `summary`, `plot` etc.

How it looks:

```
> subset(ox,as.integer(item)<3)
     meth item repl    y
1      CO    1    1 78.0
2      CO    1    2 76.4
3      CO    1    3 77.2
4      CO    2    1 68.7
5      CO    2    2 67.6
6      CO    2    3 68.3
184 pulse    1    1 71.0
185 pulse    1    2 72.0
186 pulse    1    3 73.0
187 pulse    2    1 68.0
188 pulse    2    2 67.0
189 pulse    2    3 68.0
```

```
> subset(to.wide(ox),as.integer
Note:
 Replicate measurements are t
  item repl  id   CO pulse
1    1    1 1.1 78.0    71
2    1    2 1.2 76.4    72
3    1    3 1.3 77.2    73
4    2    1 2.1 68.7    68
5    2    2 2.2 67.6    67
6    2    3 2.3 68.3    68
```

Getting your own data into R

Take a look in "The **R** Primer" by Claus Ekstrøm, or:

If your data are not too large, the simplest is to edit your data in Excel or some other spreadsheet to look like this:

```
item repl  id   CO pulse
   1    1 1.1 78.0    71
   1    2 1.2 76.4    72
   1    3 1.3 77.2    73
   2    1 2.1 68.7    68
   2    2 2.2 67.6    67
   2    3 2.3 68.3    68
```

The first line is variable names; the following lines are data.

Analysis options in this course

- Scatter plots.
- Bland-Altman plots ($(y_2 - y_1)$ vs. $(y_1 + y_2)/2$)
- Limits of Agreement (LoA).
- Models with constant bias.
- Models with linear bias.
- Conversion formulae between methods (single replicates)
- Transformation of measurements.
- Plots of conversion equations.
- Reporting of variance components.

Requirements

- **R** for data manipulation and graphics.
- Keep a script of what you did:
  - Use the built-in editor in **R**
  - the nerds can use `ESS`
  - or you can download **R**-Studio.
- You need the packages:
  - `MethComp`
  - `R2WinBUGS`
  - `coda`
  - `BRugs`
  - `Epi` - **Version 1.10 !!!**

Functions in the `MethComp` package

5 broad categories of functions in `MethComp`:

- Graphical — exploring data.
- Data manipulation — reshaping and changing.
- Simulation — generating datasets or replacing variables.
- Analysis functions — fitting models to data.
- Reporting functions — displaying results from analyses.

Overview of these in the Practicals.

Does it work?

```
library(MethComp)
library(help=MethComp) # Do you have version 1.10??
data(ox)
ox <- Meth(ox)
summary(ox)
plot(ox)
BA.plot(ox)
BA.est(ox)
( AR.ox <- AltReg(ox,linked=TRUE,trace=TRUE) )
MCmcmc(ox,code.only=TRUE)
MC.ox <- MCmcmc(ox,n.iter=100)
MethComp(MC.ox)
plot(MC.ox)
trace.MCmcmc(MC.ox)
post.MCmcmc(MC.ox)
```

Non-constant difference
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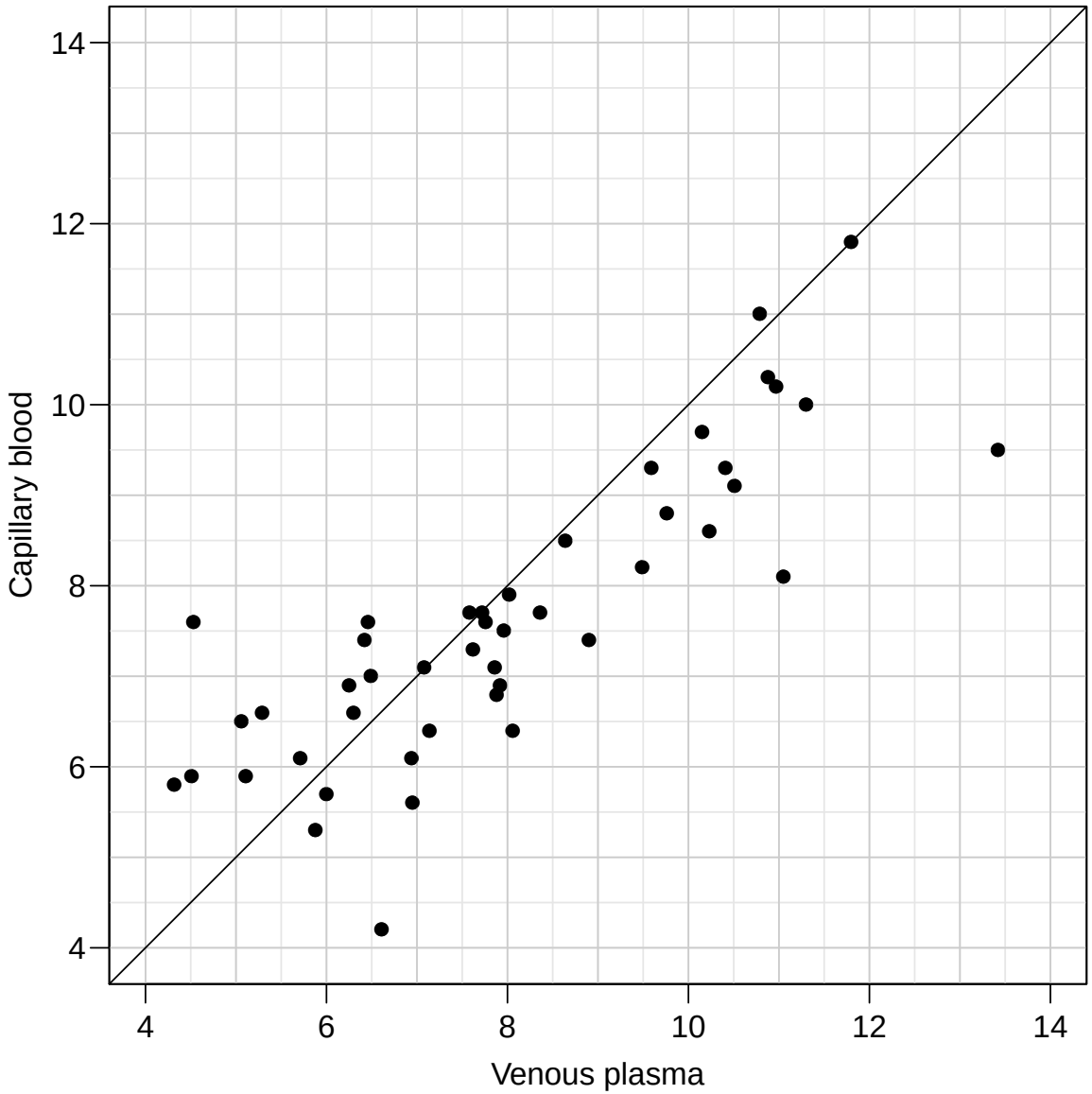
Limits of agreement — assumptions

- The difference between methods is constant
- The variances of the methods (and hence of the difference) is constant.

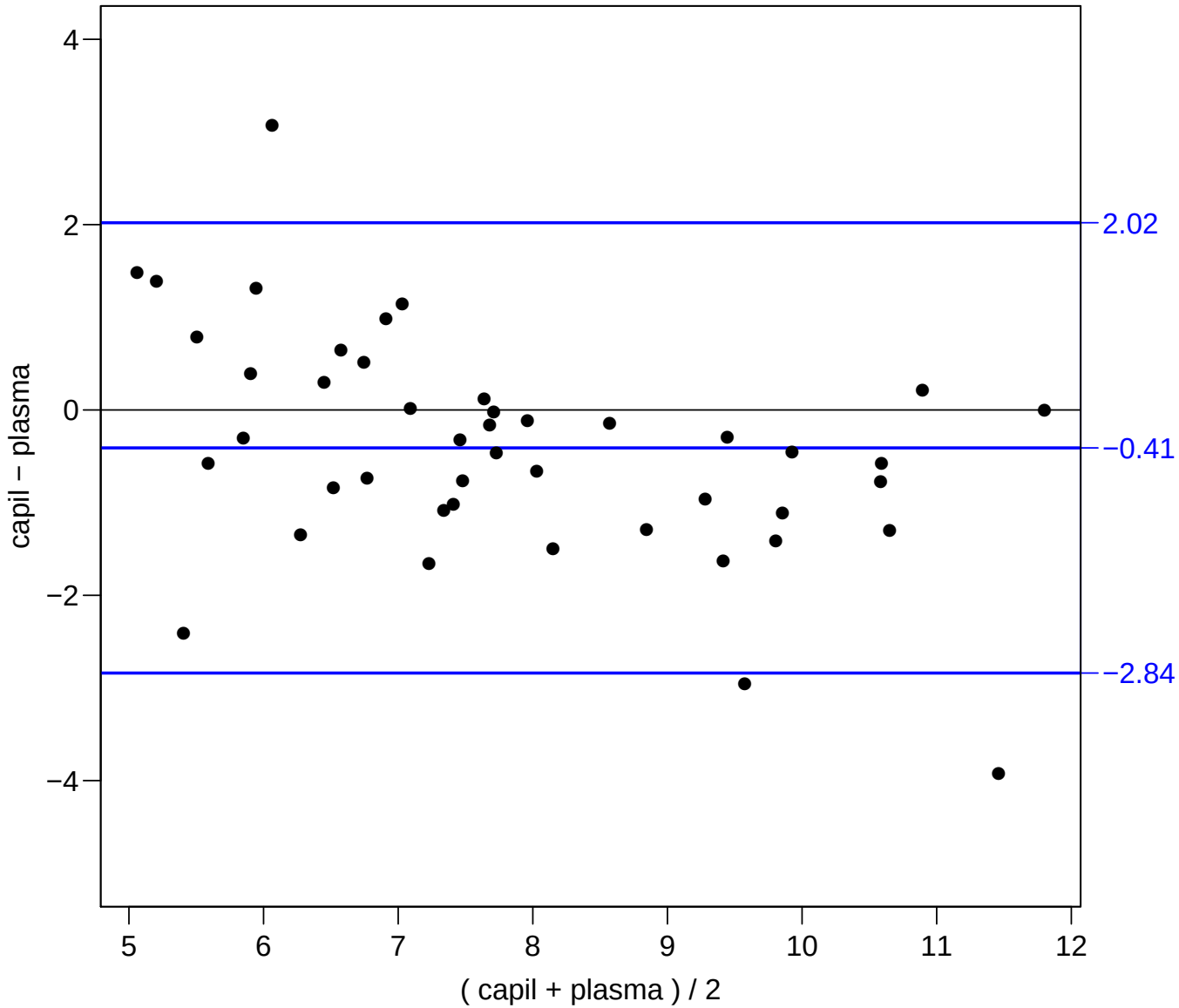
Check this by:

- Regress differences on averages.
- Regress absolute residuals from this on the averages.

Glucose measurements



Glucose measurements



Regress difference on average

$$D_i = a + bA_i + e_i, \quad \text{var}(e_i) = \sigma_D^2$$

If b is different from 0, we could use this equation to derive LoA:

$$a + bA_i \pm 2\sigma_D$$

or convert to prediction as for LoA:

$$y_{2|1} = y_1 + a + bA_i \approx y_1 + a + by_1 = a + (1 + b)y_1$$

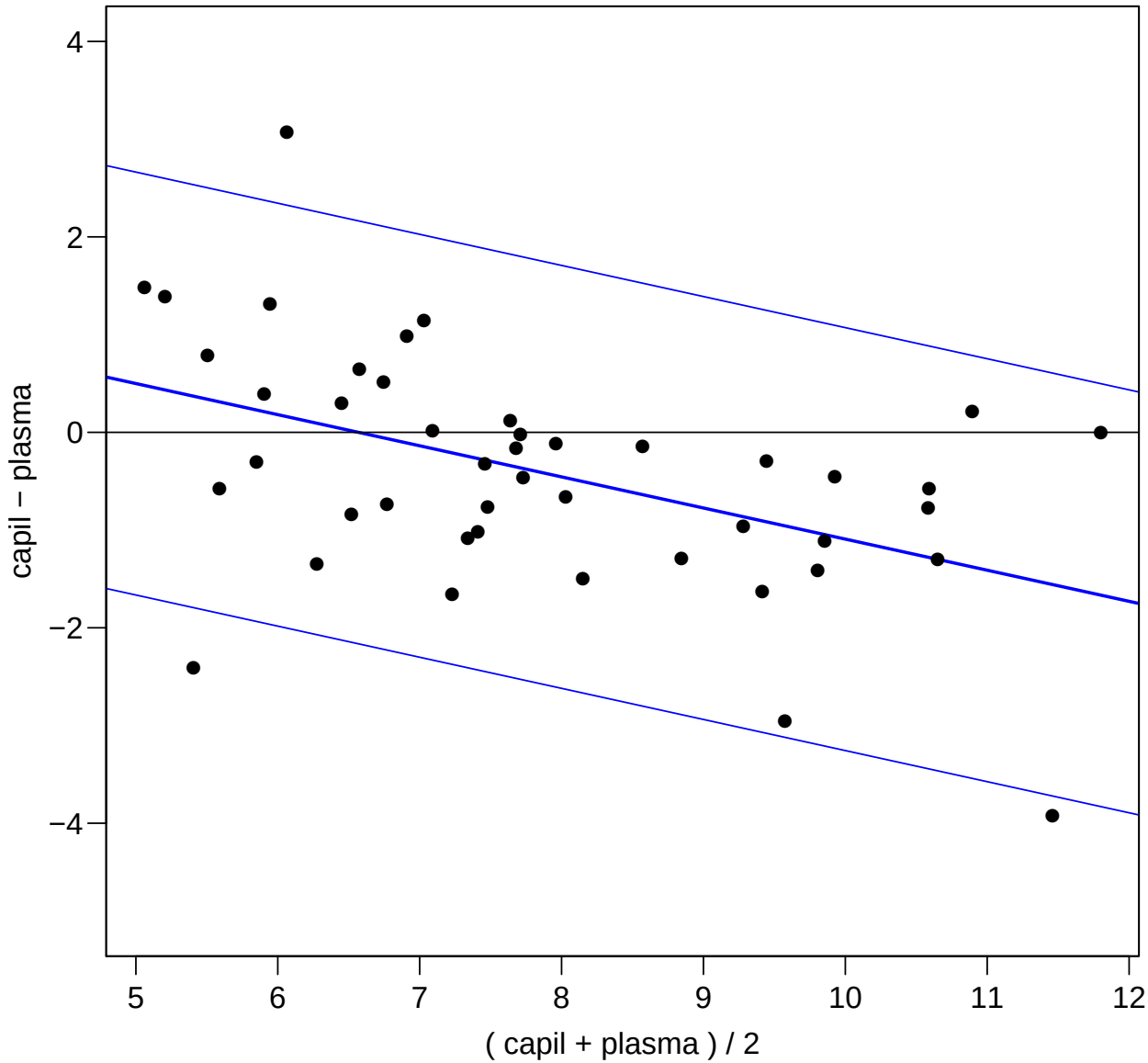
Exchanging methods would give:

$$y_{1|2} = -a + (1 - b)y_1$$

instead of:

$$y_{1|2} = \frac{-a}{1+b} + \frac{1}{1+b}y_1$$

Variable limits of agreement



Improving the regression of D on A

$$y_{2i} - y_{1i} = a + b(y_{1i} + y_{2i})/2 + e_i$$

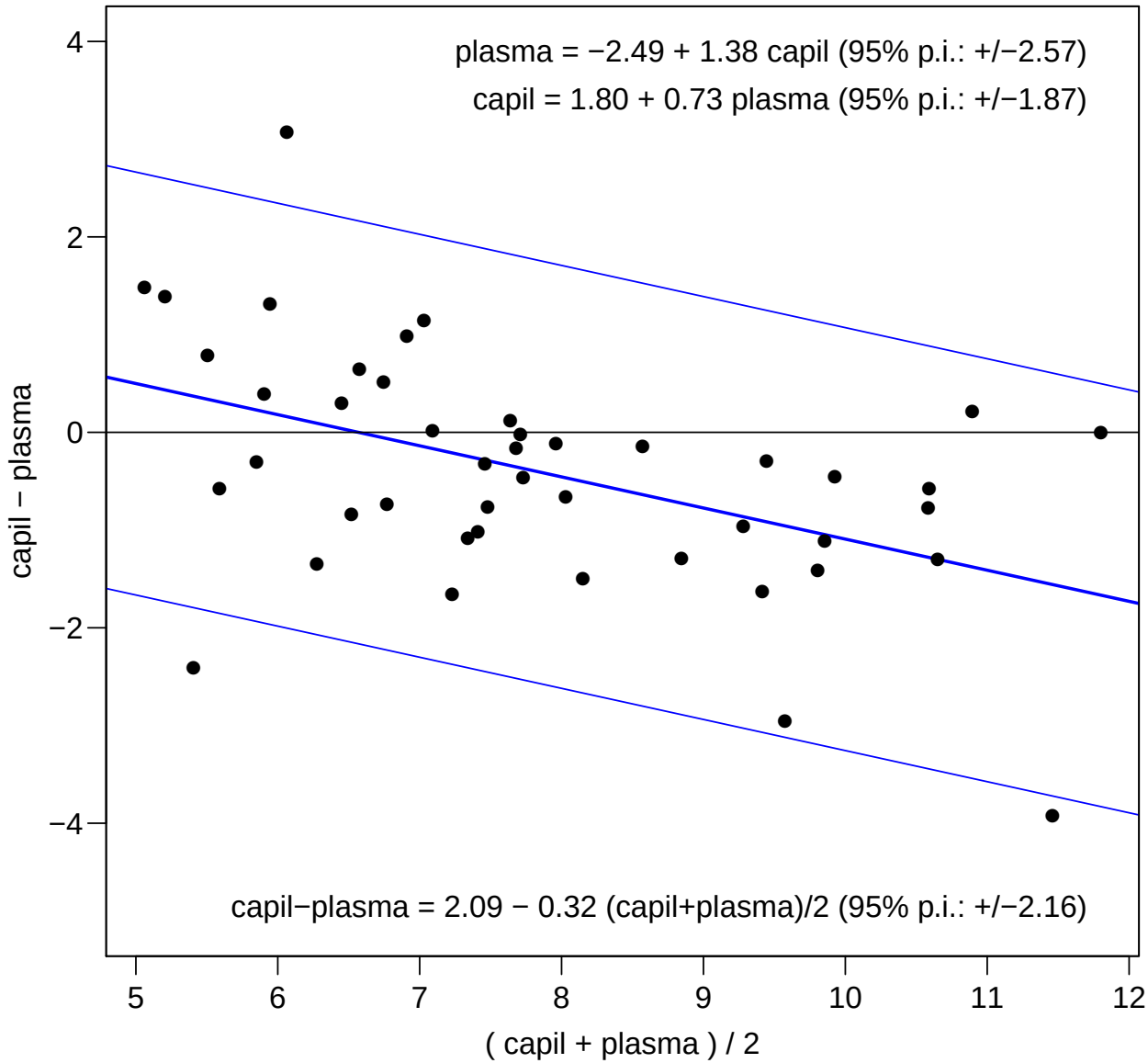
$$y_{2i}(1 - b/2) = a + (1 + b/2)y_{1i} + e_i$$

$$y_{2i} = \frac{a}{1 - b/2} + \frac{1 + b/2}{1 - b/2} y_{1i} + \frac{1}{1 - b/2} e_i$$

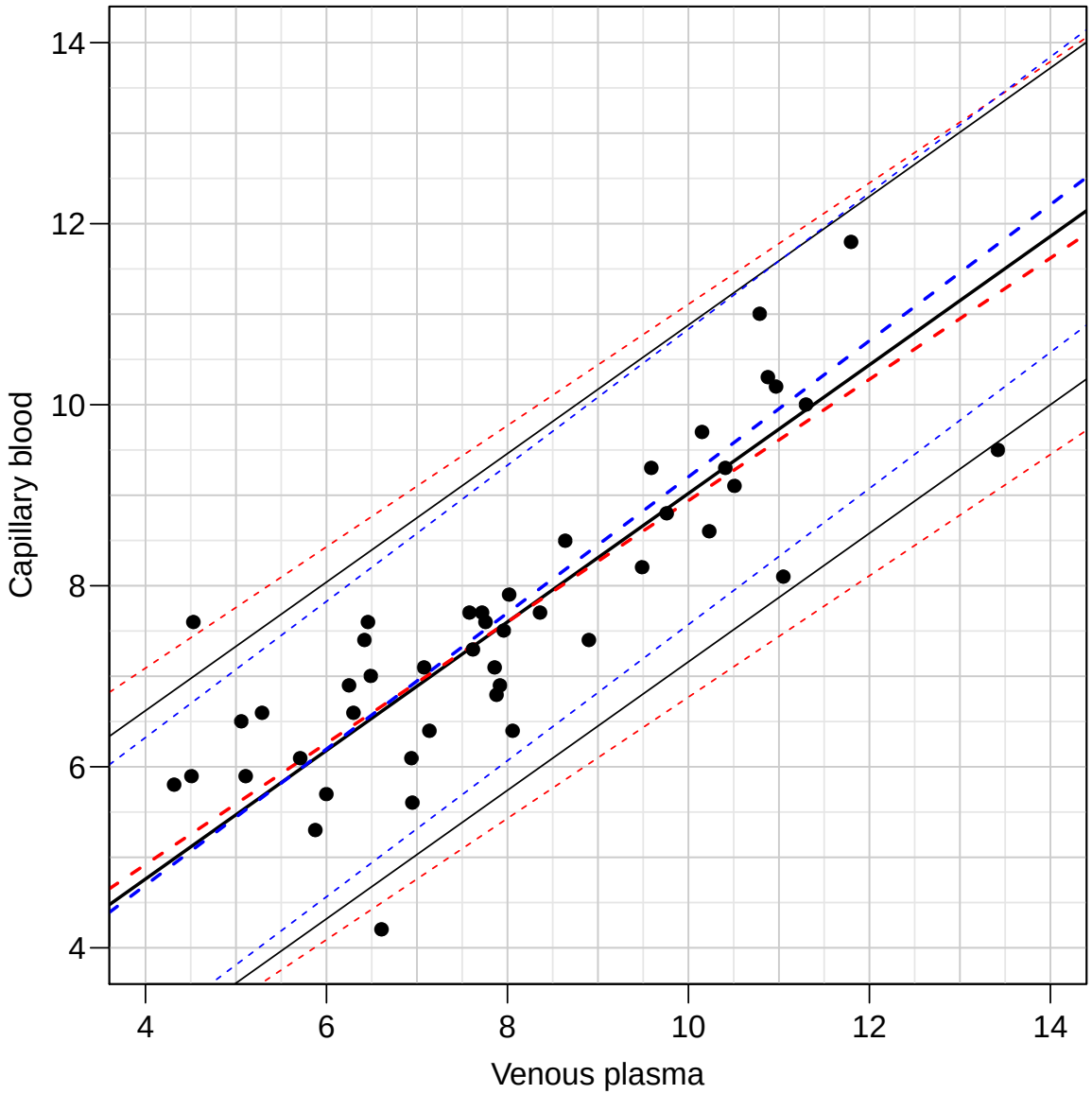
$$y_{1i} = \frac{-a}{1 + b/2} + \frac{1 - b/2}{1 + b/2} y_{2i} + \frac{1}{1 + b/2} e_i$$

This is what comes out of the functions `DA.reg` and `BA.plot`

Variable limits of agreement



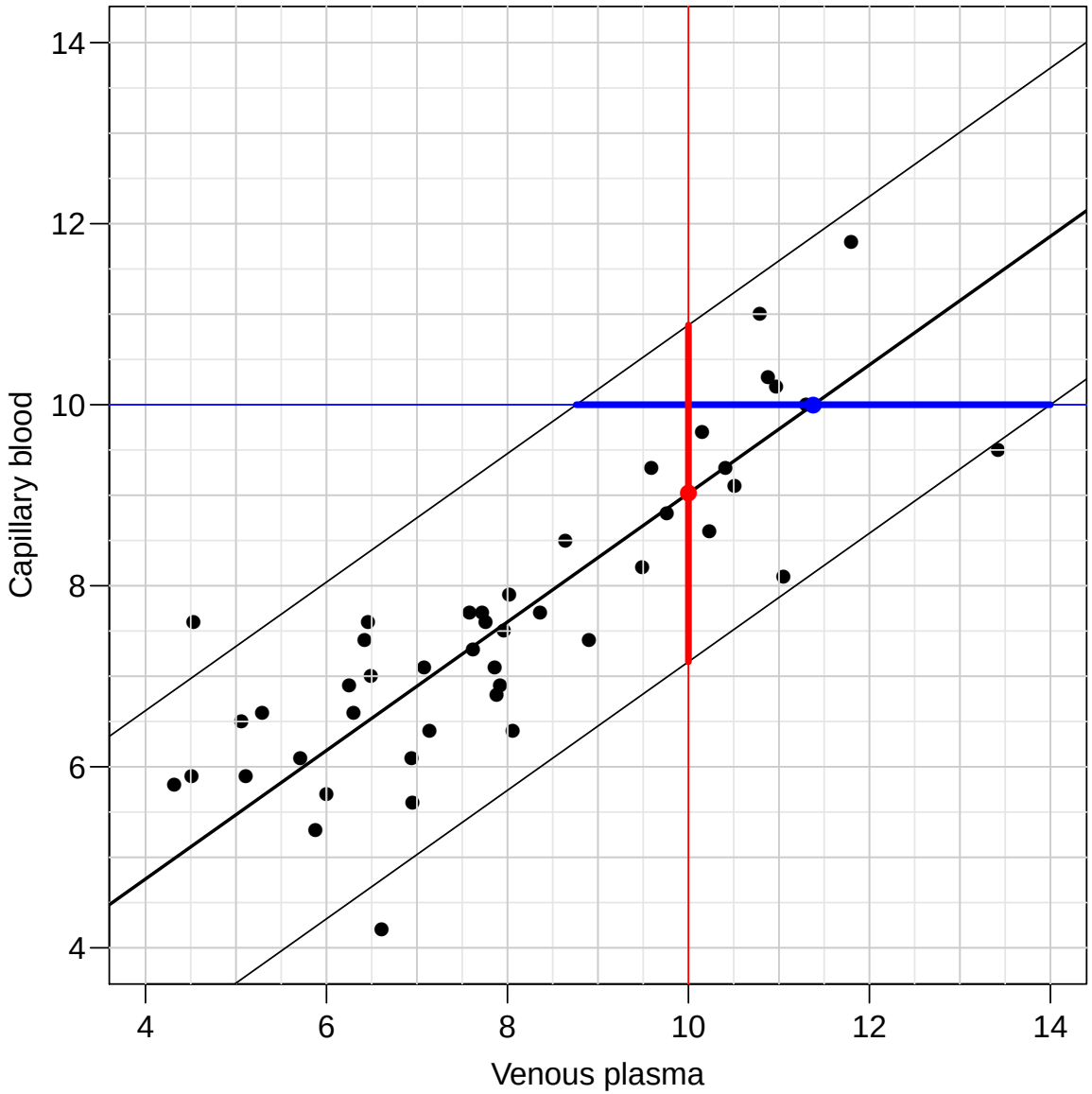
Conversion equation with prediction limits



Prediction intervals

- Prediction $\mathrm{s.e.}$ for $y_{1|2}$ is $\sigma/(1-b/2)$
- Prediction $\mathrm{s.e.}$ for $y_{1|2}$ is $\sigma/(1+b/2)$
- The slope of the prediction line is the ratio of the prediction $\mathrm{s.e.}$s.
- Hence prediction limits can be used both ways:

Conversion equation with prediction limits



Why does this work?

The general model for the data is:

$$\begin{aligned} y_{1i} &= \alpha_1 + \beta_1 \mu_i + e_{1i}, \quad e_{1i} \sim \mathcal{N}(0, \sigma_1^2) \\ y_{2i} &= \alpha_2 + \beta_2 \mu_i + e_{2i}, \quad e_{2i} \sim \mathcal{N}(0, \sigma_2^2) \end{aligned}$$

- Work out the prediction of y_1 given an observation of y_2 in terms of these parameters.
- Work out how differences relate to averages in terms of these parameters.
- Then the prediction is as we just derived it.

Why is it wrong anyway?

- Introducing linear bias, $y_{mi} = \alpha_m + \beta_m \mu_i + e_{mi}$ puts measurements by different methods on different scales.
  Hence it has formally no meaning to form the differences.
- In the induced model for $D_i \sim a + bA_i + e_i$, e_i and A_I are not independent.
- But if β is not too far from 1 it not a big problem, though.

Comparing two methods with replicate measurements
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Replicate measurements

Fat data; exchangeable replicates:

item	repl	KL	SL
1	1	4.5	4.9
1	2	4.4	5.0
1	3	4.7	4.8
3	1	6.4	6.5
3	2	6.2	6.4
3	3	6.5	6.1

Oximetry data; linked replicates:

item	repl	CO	pulse
1	1	78.0	71
1	2	76.4	72
1	3	77.2	73
2	1	68.7	68
2	2	67.6	67
2	3	68.3	68

Linked or exchangeable replicates!

Extension of the model: exchangeable replicates

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

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

Extension of the model: linked replicates

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

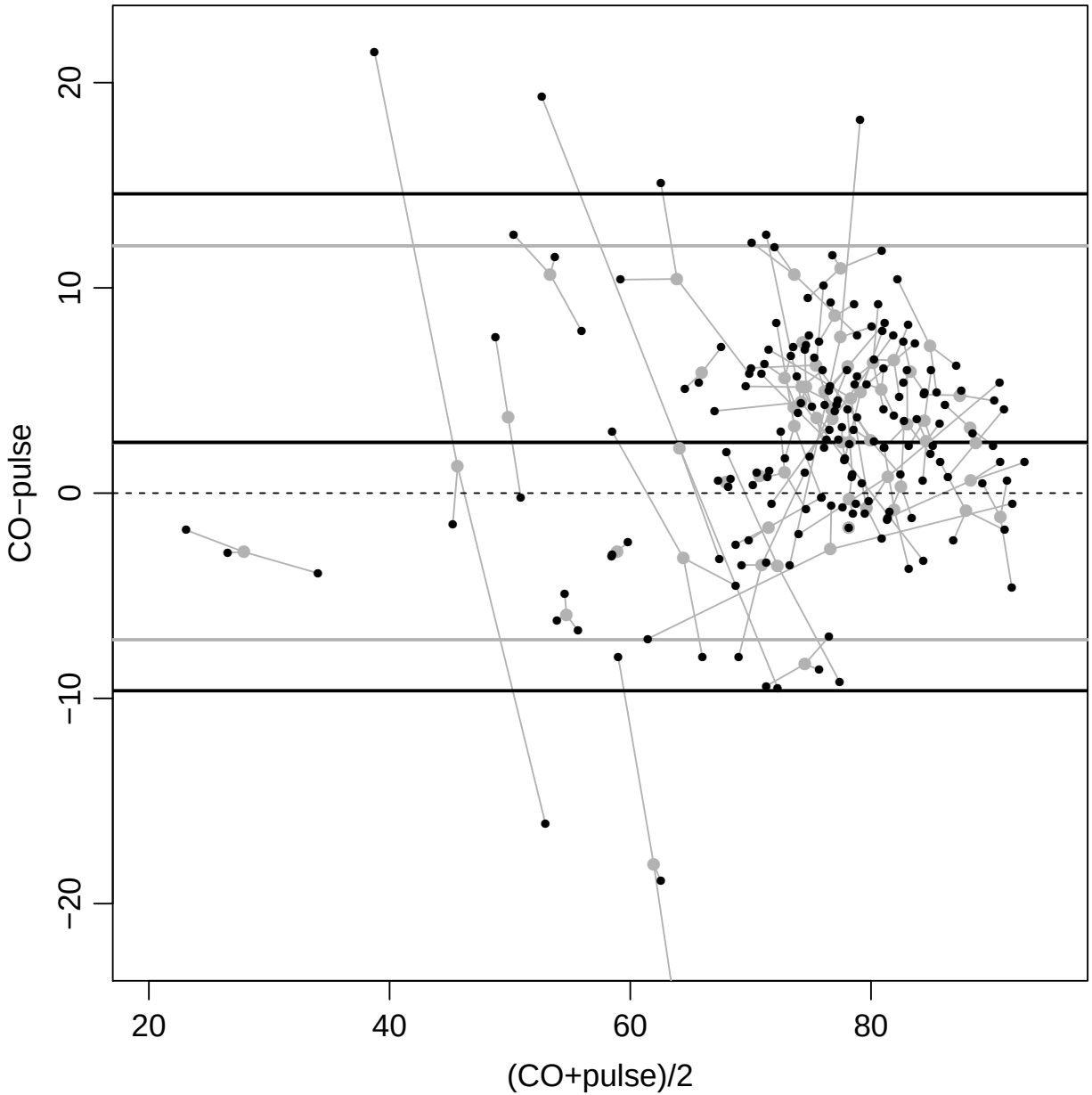
- Still assumes that the difference between methods is constant.
- Replicates are *linked* between methods: a_{ir} is common across methods, i.e. the first replicate on a person is made under similar conditions for all methods (i.e. at a specific day or the like).

Replicate measurements

Three approaches to limits of agreement with replicate measurements:

1. Take means over replicates within each method by item stratum.
2. Replicates within item are taken as items.
3. Fit the correct variance components model and use this as basis for the LoA.
   The model is fitted using:
   `> BA.est( data, linked=TRUE ).`

Oximetry data



Replicate measurements

- The limits of agreement should still be for difference between future **single** measurements.
- Analysis based on the **means** of replicates is therefore **wrong**:
- Model:

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

- $\mathrm{var}(y_{1jr} - y_{2jr}) = \tau_1^2 + \tau_2^2 + \sigma_1^2 + \sigma_2^2$
  — note that the term $a_{ir} - a_{ir}$ cancels because we are referring to the *same* replicate.

Wrong or almost right

In the model the correct limits of agreement would be:

$$\alpha_1 - \alpha_2 \pm 1.96\sqrt{\tau_1^2 + \tau_2^2 + \sigma_1^2 + \sigma_2^2}$$

But if we use means of replicates to form the differences we have:

$$\begin{aligned}\bar{d}_i = \bar{y}_{1i\cdot} - \bar{y}_{2i\cdot} &= \alpha_1 - \alpha_2 + \frac{\sum_r a_{ir}}{R_{1i}} - \frac{\sum_r a_{ir}}{R_{2i}} \\ &\quad + c_{1i} - c_{2i} + \frac{\sum_r e_{1ir}}{R_{1i}} - \frac{\sum_r e_{2ir}}{R_{2i}}\end{aligned}$$

The terms with a_{ir} are only relevant for linked replicates in which case $R_{1i} = R_{2i}$ and therefore the term vanishes. Thus:

$$\mathrm{var}(\bar{d}_i) = \tau_1^2 + \tau_2^2 + \sigma_1^2/R_{1i} + \sigma_2^2/R_{2i} < \tau_1^2 + \tau_2^2 + \sigma_1^2 + \sigma_2^2$$

so the limits of agreement calculated based on the means are much too narrow as prediction limits for differences between future *single* measurements.

(Linked) replicates as items

If replicates are taken as items, then the calculated differences are:

$$d_{ir} = y_{1ir} - y_{2ir} = \alpha_1 - \alpha_2 + c_{1i} - c_{2i} + e_{1ir} - e_{2ir}$$

which has variance $\tau_1^2 + \tau_2^2 + \sigma_1^2 + \sigma_2^2$, and so gives the correct limits of agreement. However, the differences are not independent:

$$\mathrm{cov}(d_{ir}, d_{is}) = \tau_1^2 + \tau_2^2$$

Negligible if the residual variances are very large compared to the interaction, variance likely to be only slightly downwards biased.

Recommendations

- Fit the correct model, and get the estimates from that, e.g. by using `BA.est`.
- If you must use over-simplified methods:
- Use linked replicates as item.
- If replicates are not linked; make a random linking.
  Note: If this give a substantially different picture than using the original replicate numbering as linking key, there might be something fishy about the data.

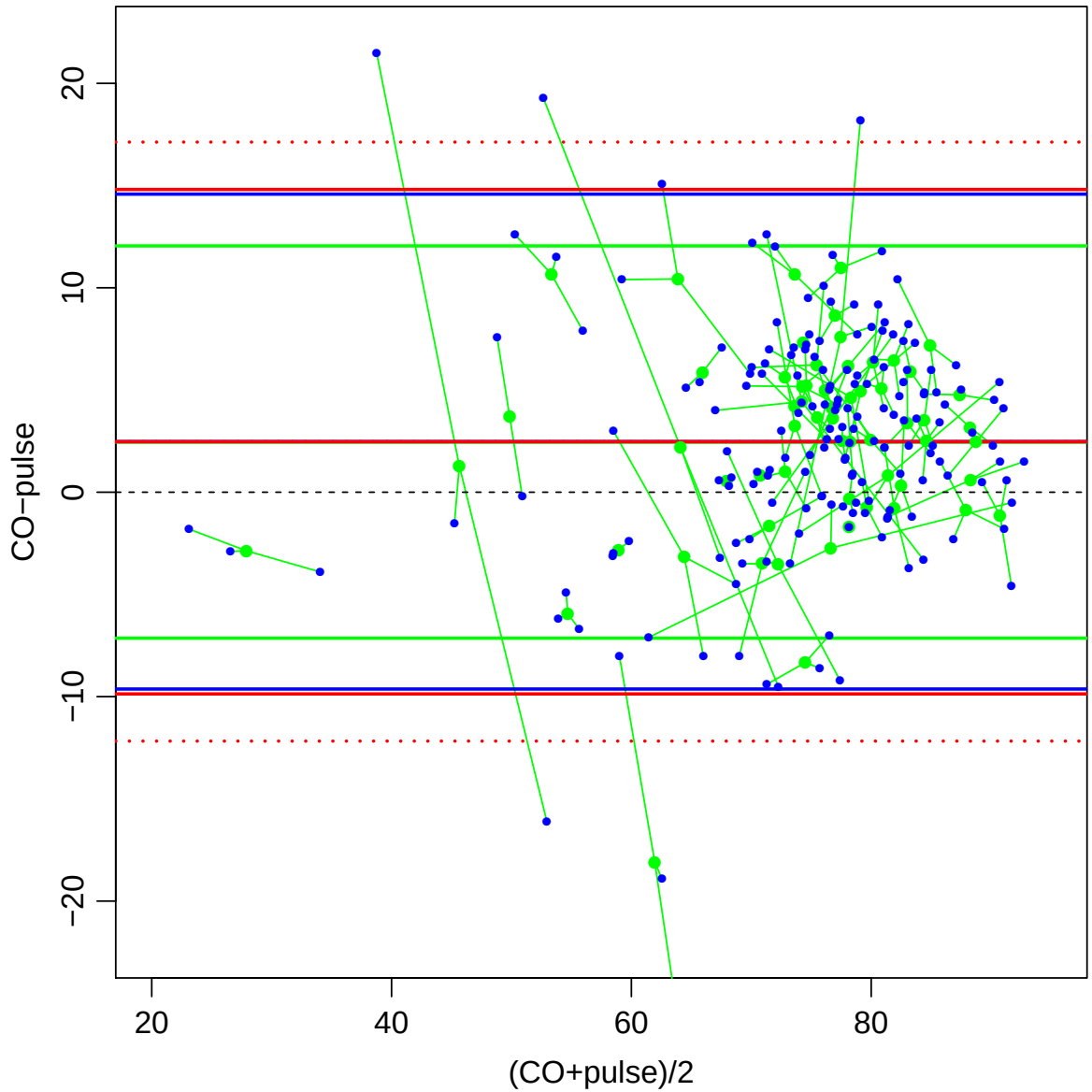
Further details, see [3].

Oximetry data

Linked replicates used as items

Mean over replicates as items

Limits based on model — dashed line assuming exchangeable replicates



Repeatability and reproducibility

Wednesday 9 February, morning

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Accuracy of a measurement method

- Repeatability:
  The accuracy of the method under exactly similar circumstances; i.e. the same lab, the same technician, and the same day.
  (**Repeata**bility conditions)
- Reproducibility:
  The accuracy of the method under comparable circumstances, i.e. the same machinery, the same kit, but possibly different days or laboratories or technicians.
  (**Reproduci**bility conditions)

Quantification of accuracy

- Upper limit of a 95% confidence interval for the difference between two measurments.
- Suppose the variance of the measurement is σ^2:

$$\mathrm{var}(y_{mi1} - y_{mi2}) = 2\sigma^2$$

i.e the standard error is $\sqrt{2}\sigma$, and a confidnece interval for the difference:

$$0 \pm 1.96 \times \sqrt{2}\sigma = 0 \pm 2.772\sigma \approx 2.8\sigma$$

- This is called the reproducibility coefficient or simply the reproducibility. (The number 2.8 is used as a convenient approximation).

Quantification of accuracy

- Where do we get the σ?
- Repeat measurements on the same item (or even better) several items.
- The conditions under which the repeat (replicate) measurements are taken determines whether we are estimating repeatability or reproducibility.
- In larger experiments we must consider the **exchangeability** of the replicates — i.e. which replicates are done under (exactly) similar conditions and which are not.

Linear bias between methods
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Extension with non-constant bias

$$y_{mir} = \alpha_m + \beta_m \mu_i + \text{random effects}$$

There is now a *scaling* between the methods.

Methods do not measure on the same scale — the relative scaling is *estimated*, between method 1 and 2 the scale is β_2/β_1.

Consequence: Multiplication of all measurements on one method by a fixed number does not change results of analysis:

The corresponding β is multiplied by the same factor as is the variance components for this method.

Variance components

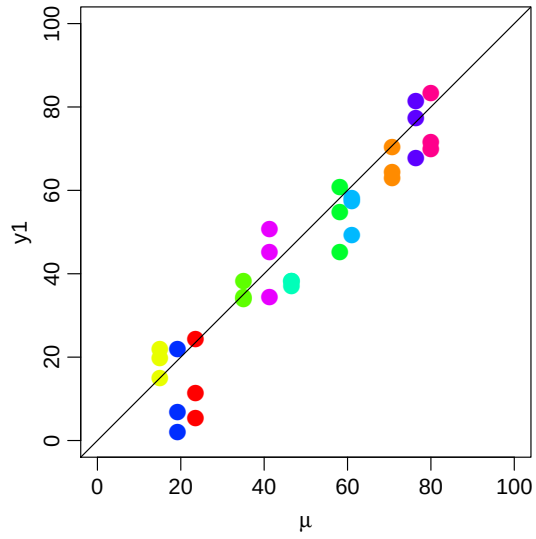
Two-way interactions:

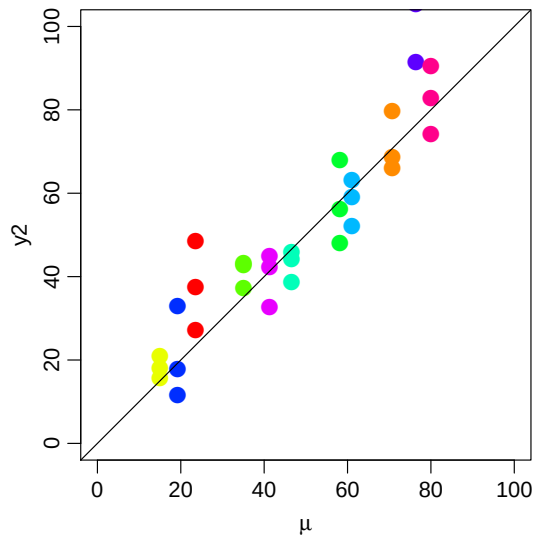
$$y_{mir} = \alpha_m + \beta_m(\mu_i + a_{ir} + c_{mi}) + e_{mir}$$

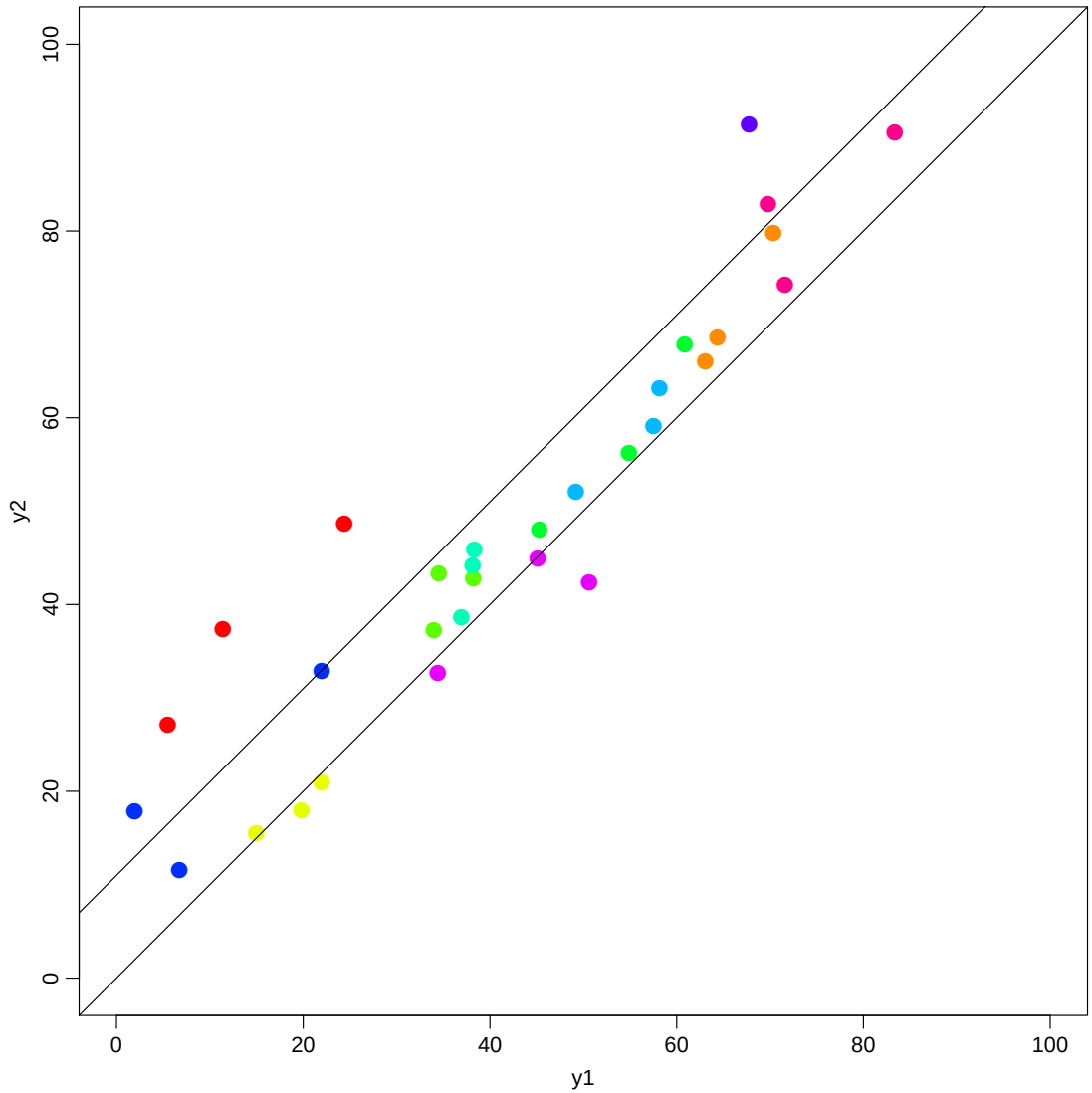
The random effects c_{mi} and e_{mir} have variances specific for each method.

But a_{ir} does not depend on m — must be scaled to each of the methods by the corresponding β_m.

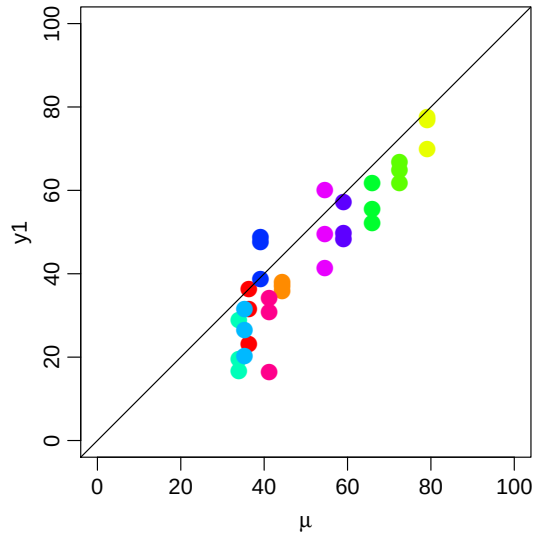
Implies that $\omega = \mathrm{s.d.}(a_{ir})$ is irrelevant — the scale is arbitrary. The relevant quantities are $\beta_m\omega$ — the between replicate variation within item *as measured on the mth scale*.

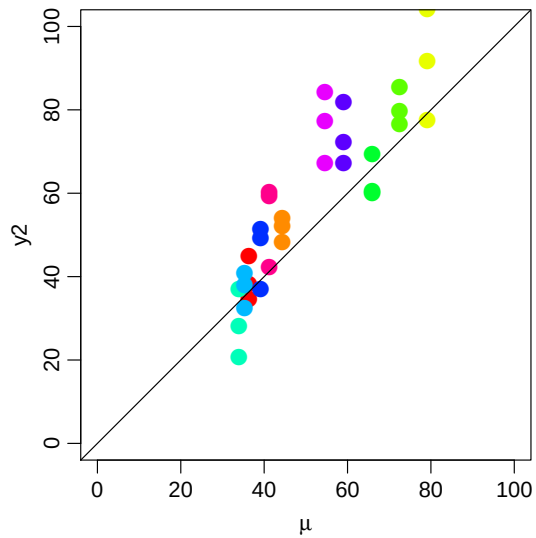


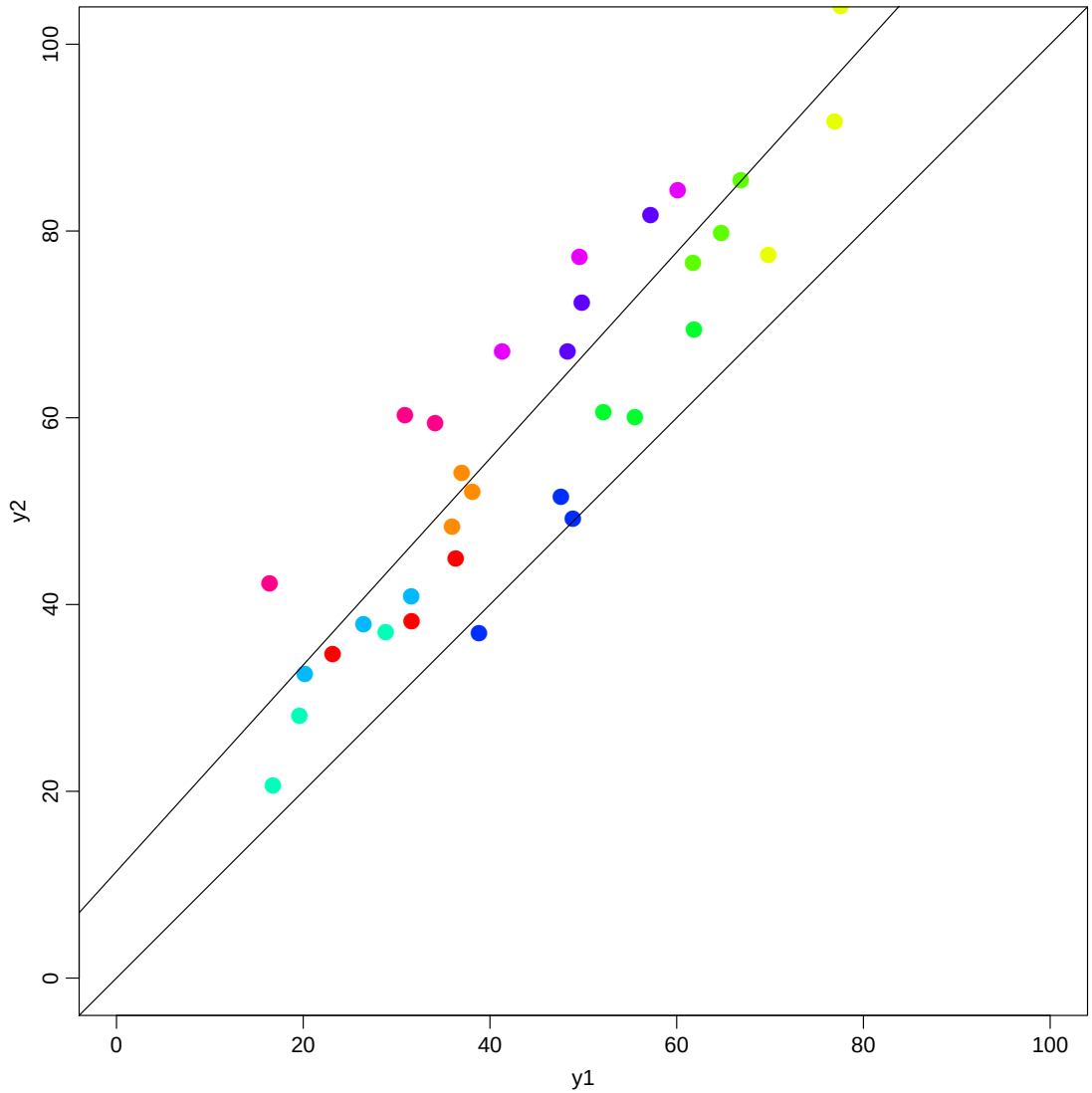




$$y_{mir} = \alpha_m + \mu_i + a_{ir} + c_{mi} + e_{mir}$$







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

Estimation: Alternating random effects regression
Morning

Bendix Carstensen

MethComp
28 September 2011
Tutorial, SISMEC, Ancona, Italy

`http://BendixCarstensen.com/MethComp/Ancona.2011`

Alternating random effects regression

Carstensen [4] proposed a ridiculously complicated approach to fit the model

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

based in the observation:

- For fixed μ the model is a linear mixed model.
- For fixed (α, β) it is a regression through 0.

This has be improved in [5]

Alternating random effects regression

Now consider instead the correctly formulated version of the slightly more general model:

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

Here we observe

- For fixed $\zeta_{mir} = \mu_i + a_{ir} + c_{mi}$ the model is a linear model, with residual variances different between methods.
- For fixed (α, β) scaled responses y are used:

$$\frac{y_{mir} - \alpha_m}{\beta_m} = \mu_i + a_{ir} + c_{mi} + e_{mir}/\beta_m$$

Estimation algorithm

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

1. Start with $\zeta_{mir} = \bar{y}_{mi\cdot}$
2. Estimate (α_m, β_m).
3. Compute the scaled responses and fit the random effects model.
4. Use the estimated μ_is, and BLUPs of a_{ir} and c_{mi} to update ζ_{mir}.
5. Check convergence in terms of identifiable parameters.

The residual variances

- The variance components are estimated in the model for the scaled response.
- The parameters (α_m, β_m) are not taken into account in the calculation of the residual variance.
- Hence the residual variances must be corrected *post hoc*.
- This machinery is implemented in the function `AltReg` in the `MethComp` package.

```
> AR.ox <- AltReg(ox,linked=T,trace=T)
AltReg uses 354 obs. out of 354 in the supplied data.

iteration 1 criterion: 1
       alpha  beta sigma Intercept: CO  pulse Slope: CO pulse Ix
CO     0.911 0.988 1.861         74.419 74.417      1.000 0.974
pulse -1.039 1.014 1.860         74.422 74.419      1.027 1.000
...

iteration 14 criterion: 0.000986339
        alpha  beta sigma Intercept: CO  pulse Slope: CO pulse I
CO    -20.548 1.281 1.027         74.419 76.938      1.000 1.063
pulse -17.301 1.205 3.308         72.049 74.419      0.941 1.000
There were 14 warnings (use warnings() to see them)

> round(AR.ox,3)
    From
To  Intercept: CO  pulse Slope: CO pulse IxR sd. MxI sd. res.sd.
  CO          0.000 -2.159      1.000 1.063    3.521    2.978    2.055
  pulse       2.031  0.000      0.941 1.000    3.313    2.802    4.079
```

Your turn:

Start on the practical titled:

"Oximetry: Linked replicates with non-constant bias"

Converting between methods
Afternoon

Bendix Carstensen

MethComp
28 September 2011
Tutorial, SISMEC, Ancona, Italy

`http://BendixCarstensen.com/MethComp/Ancona.2011`

Predicting method 2 from method 1

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

The random effects have expectation 0, so:

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

$$
\begin{aligned}
y_{20r} &= \alpha_2 + \frac{\beta_2}{\beta_1}(y_{10r} - \alpha_1 - e_{10r}) \\
&\qquad + \beta_2(-c_{10} + c_{20}) + e_{20r} \\
\mathrm{var}(\hat{y}_{20}|y_{10}) &= \left(\frac{\beta_2}{\beta_1}\right)^2(\beta_1^2\tau_1^2 + \sigma_1^2) + (\beta_2^2\tau_2^2 + \sigma_2^2)
\end{aligned}
$$

The slope of the prediction line from method 1 to method 2 is β_2/β_1.

The width of the prediction interval is:

$$
2 \times 2 \times \sqrt{\left(\frac{\beta_2}{\beta_1}\right)^2(\beta_1^2\tau_1^2 + \sigma_1^2) + (\beta_2^2\tau_2^2 + \sigma_2^2)}
$$

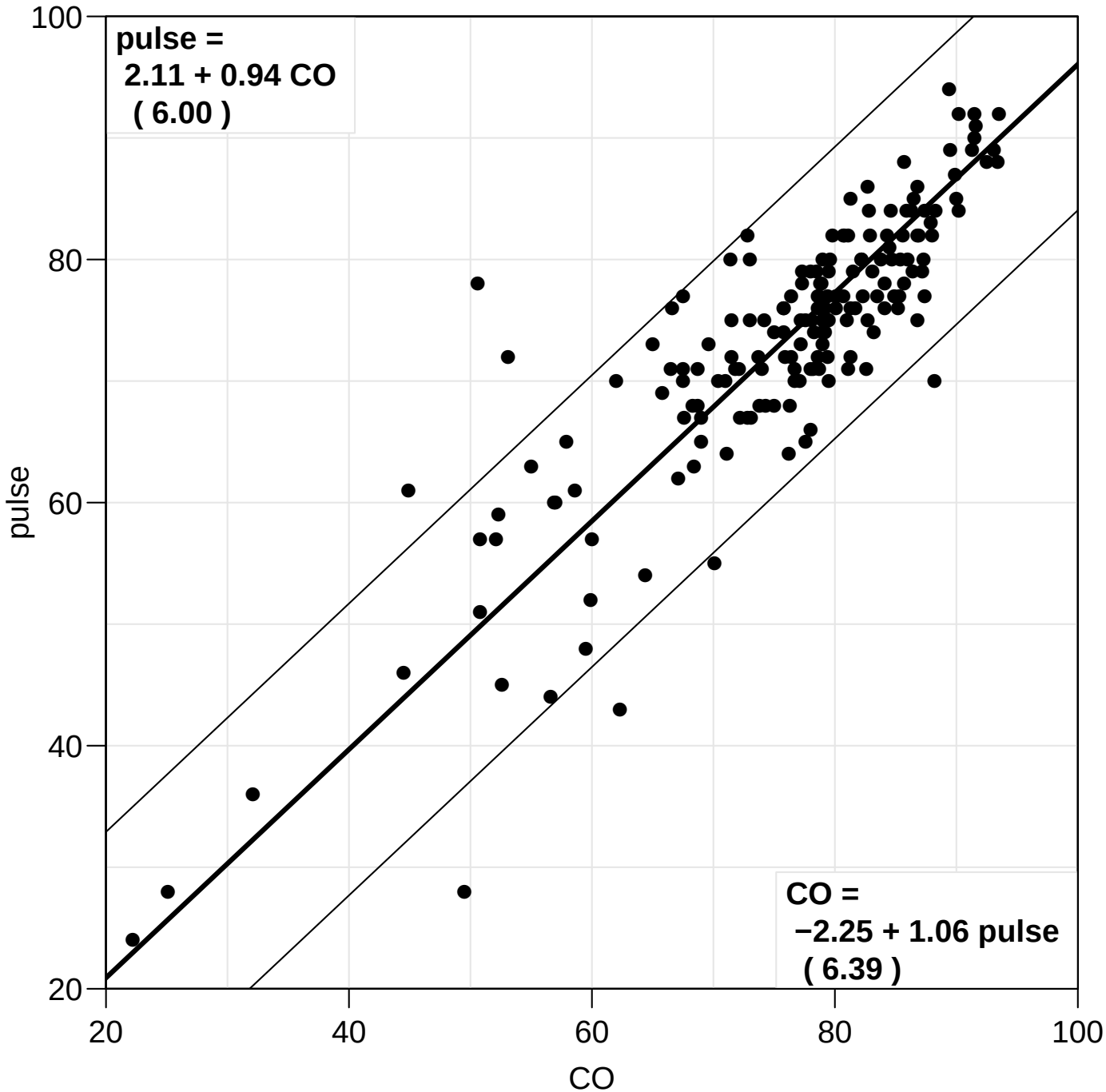
If we do the prediction the other way round $(y_1|y_2)$ we get the same relationship i.e. a line with the inverse slope, β_1/β_2.

The width of the prediction interval in this direction is (by permutation of indices):

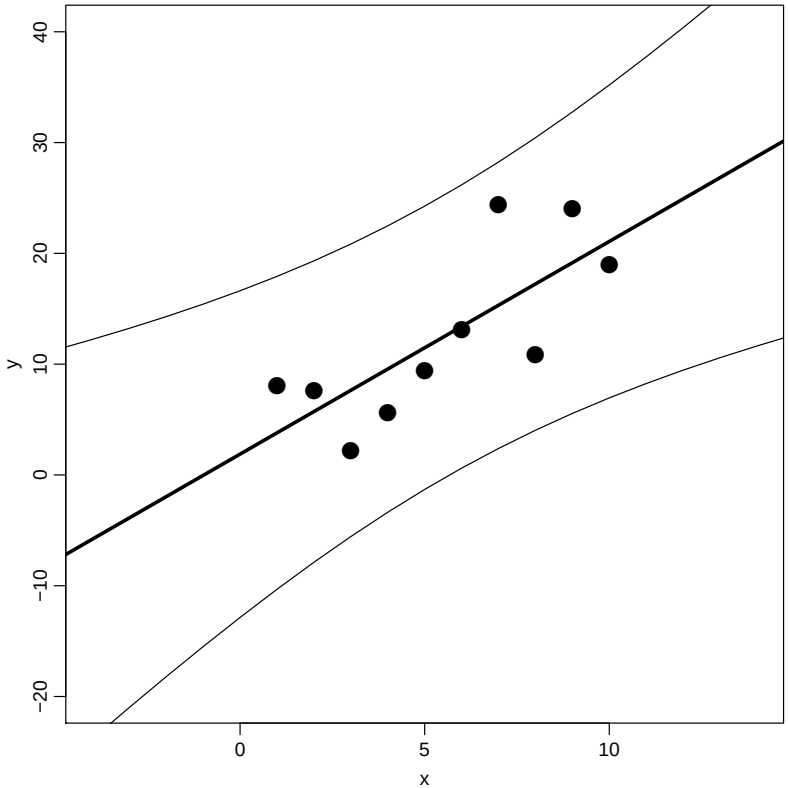
$$2 \times 2 \times \sqrt{(\beta_1^2\tau_1^2 + \sigma_1^2) + \left(\frac{\beta_1}{\beta_2}\right)^2(\beta_2^2\tau_2^2 + \sigma_2^2)}$$

$$= 2 \times 2 \times \frac{\beta_1}{\beta_2}\sqrt{\left(\frac{\beta_2}{\beta_1}\right)^2(\beta_1^2\tau_1^2 + \sigma_1^2) + (\beta_2^2\tau_2^2 + \sigma_2^2)}$$

i.e. if we draw the prediction limits as straight lines they can be used both ways.


pulse =
2.11 + 0.94 CO
(6.00)
CO =
−2.25 + 1.06 pulse
(6.39)
pulse
CO
100
80
60
40
20
20
40
60
80
100

What happened to the curvature?



Usually the prediction limits are curved:

$$\hat{y}|x \pm t_{0.975} \times \hat{\sigma}\sqrt{1 + x'x}$$

In our prediction we have ignored the last term $(x'x)$, i.e. effectively assuming that there is no estimation error on $\alpha_{2|1}$ and $\beta_{2|1}$.

Transformation of data
Afternoon

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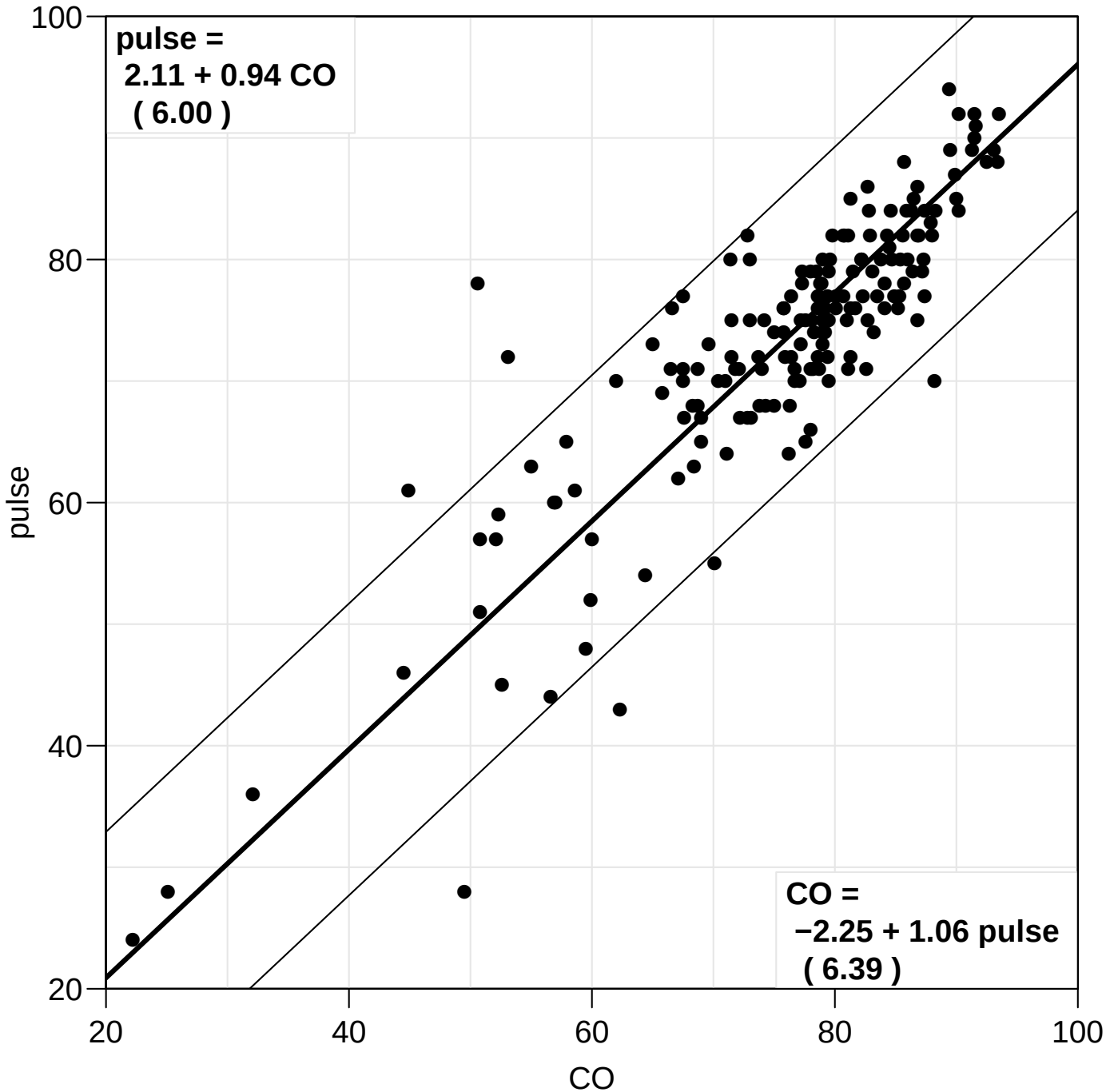
If variances are not constant

A transformation might help:

```
> round( ftable( DA.reg(ox) ), 3 )
               alpha   beta sd.pred beta=1 s.d.=K
From: To:
CO    CO       0.000  1.000      NA     NA      NA
      pulse    1.864  0.943   5.979  0.142   0.000
pulse CO      -1.977  1.061   6.342  0.142   0.000
      pulse    0.000  1.000      NA     NA      NA

> oxt <- transform( ox, y=log(y/(100-y)) )

> round( ftable( DA.reg(oxt) ), 3 )
               alpha   beta sd.pred beta=1 s.d.=K
From: To:
CO    CO       0.000  1.000      NA     NA      NA
      pulse   -0.034  0.900   0.306  0.009   0.246
pulse CO       0.038  1.111   0.340  0.009   0.246
      pulse    0.000  1.000      NA     NA      NA
```


pulse =
2.11 + 0.94 CO
(6.00)
CO =
−2.25 + 1.06 pulse
(6.39)
pulse
CO
100
80
60
40
20
20
40
60
80
100

Analysis on the transformed scale

```
> ARoxt <- AltReg( ox, linked=T, trace=T, Transform="pctlogit" )

iteration 1 criterion: 1
       alpha  beta sigma Intercept: CO pulse Slope: CO pulse   I
CO     0.003 0.998 0.098          1.151 1.151     1.000 0.994 0.2
pulse -0.003 1.003 0.098          1.151 1.151     1.006 1.000 0.2

iteration 2 criterion: 0.08547255
       alpha  beta sigma Intercept: CO pulse Slope: CO pulse   I
CO    -0.024 1.032 0.100          1.151 1.181     1.000 1.013 0.2
pulse -0.039 1.019 0.121          1.121 1.151     0.987 1.000 0.2

...

iteration 15 criterion: 0.0008526646
       alpha  beta sigma Intercept: CO pulse Slope: CO pulse   I
CO    -0.528 1.506 0.082          1.151 1.314     1.000 1.105 0.2
pulse -0.516 1.362 0.144          1.003 1.151     0.905 1.000 0.2
```

Analysis on the transformed scale

```
> ARoxt <- AltReg( ox, linked=T, trace=T, Transform="pctlogit" )

AltReg converged after  15 iterations
Last convergence criterion was  0.0008526646

> ARoxt
Note: Response transformed by:  log p/(100 - p)

 Conversion between methods:
               alpha   beta     sd
To:   From:
CO    CO       0.000  1.000  0.202
      pulse    0.042  1.105  0.341
pulse CO      -0.038  0.905  0.309
      pulse    0.000  1.000  0.271

 Variance components (sd):
         s.d.
Method    IxR   MxI   res
  CO    0.232 0.160 0.143
  pulse 0.210 0.145 0.191
```

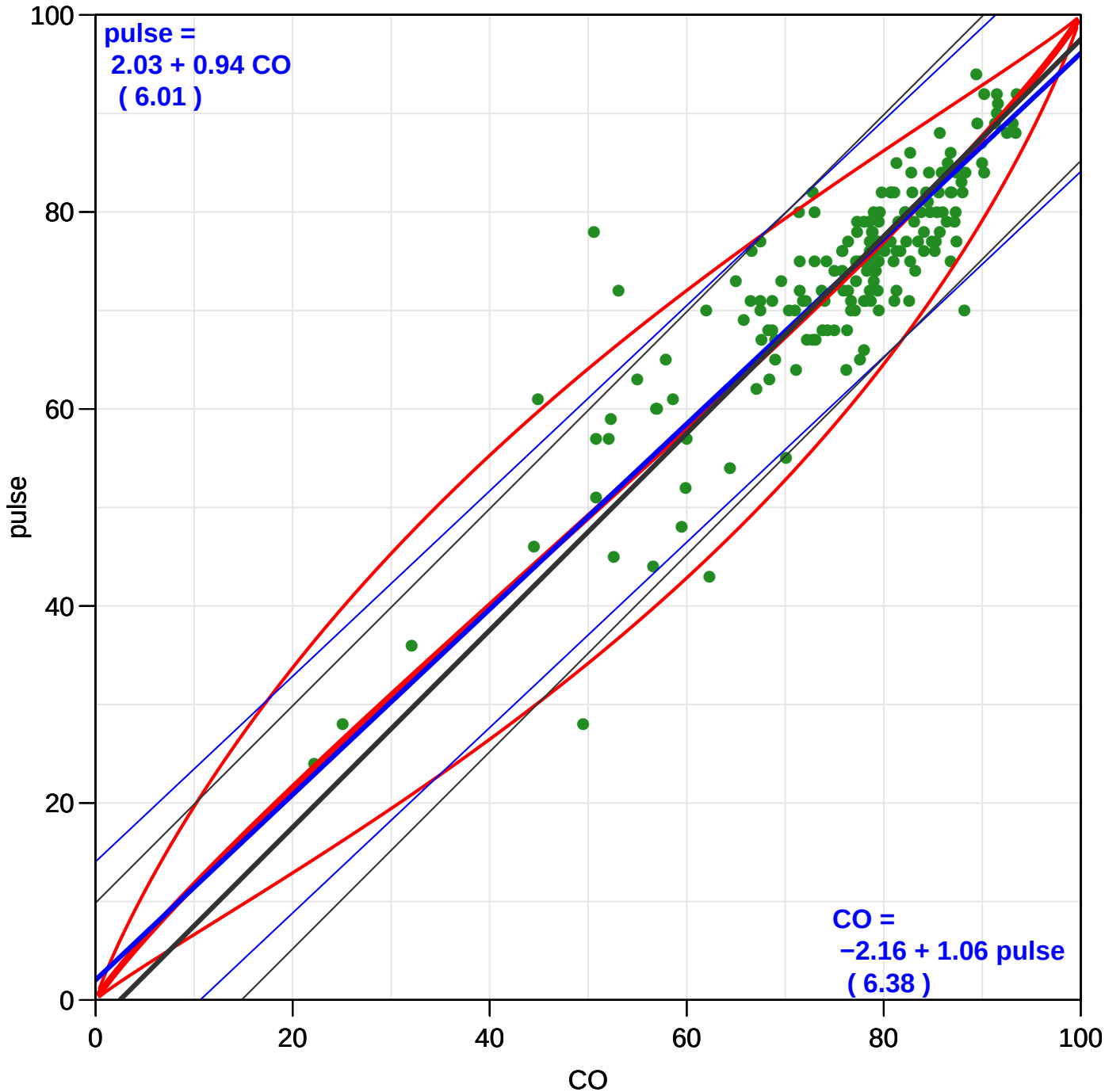
This is an analysis for the *transformed* data.

Backtransformation for plotting

```
 prpulse <- seq(20,100,1)
lprpulse <- log( prpulse / (100-prpulse) )
lprCO    <- ARoxt["CO",2] + ARoxt["CO",4]*lprpulse
lprCOlo  <- ARoxt["CO",2] + ARoxt["CO",4]*lprpulse -
                                          2*sd.CO.pred
lprCOhi  <- ARoxt["CO",2] + ARoxt["CO",4]*lprpulse +
                                          2*sd.CO.pred
 prCO    <- 100/(1+exp(-cbind( lprCO, lprCOlo, lprCOhi )))
 prCO[nrow(prCO),] <- 100
```

But this is not necessary; it is implemented in `plot.MethComp`:

```
plot( ARoxt, pl.type="conv" )
```


pulse =
2.03 + 0.94 CO
(6.01)
CO =
−2.16 + 1.06 pulse
(6.38)
pulse
CO
0
20
40
60
80
100

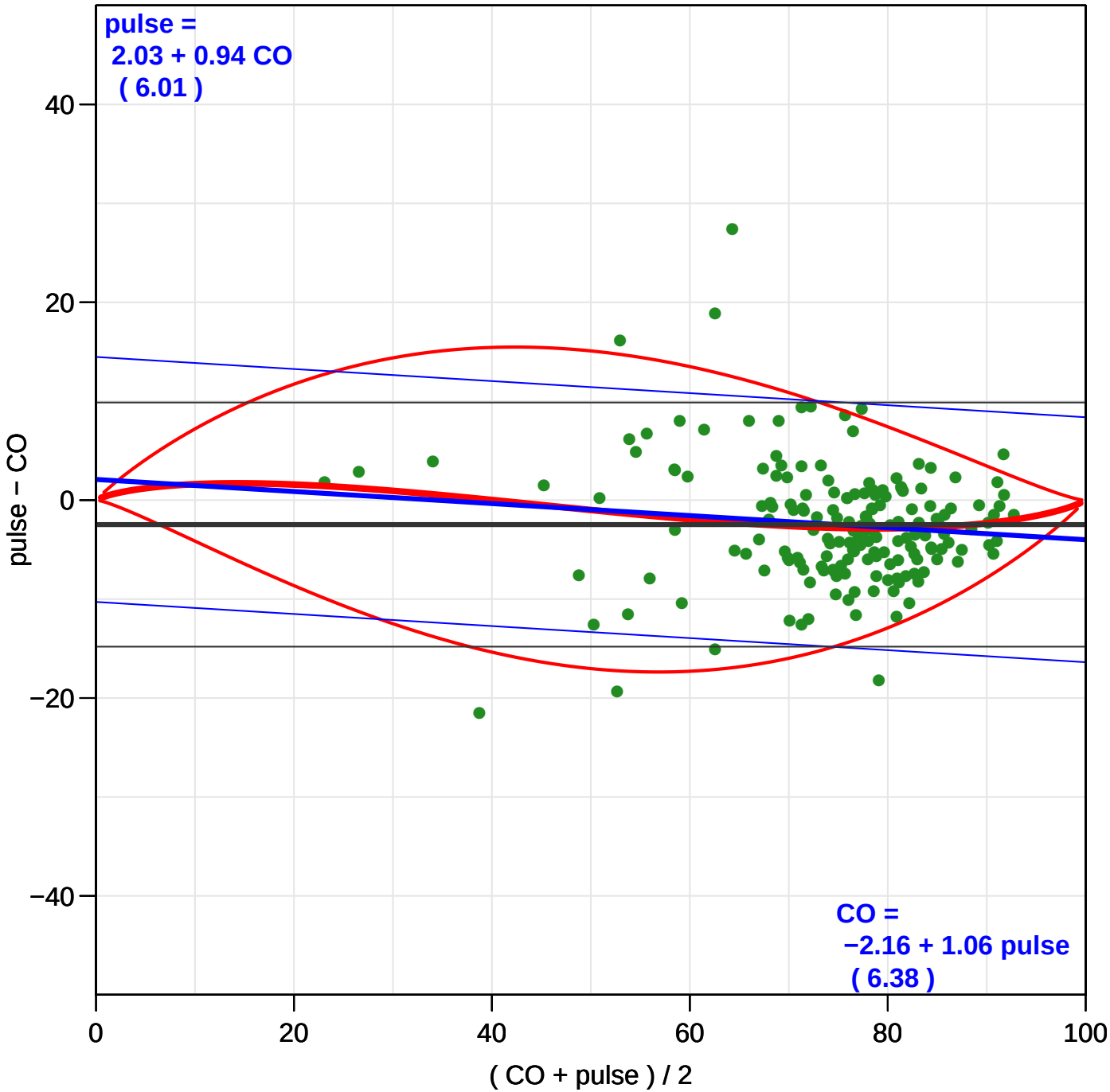
Transformation to a Bland-Altman plot

Just convert to the differences versus the averages:

```
prpulse <- cbind( prpulse, prpulse, prpulse )
with( to.wide(ox),
      plot( (CO+pulse)/2, CO-pulse, pch=16,
            ylim=c(-40,40), xlim=c(20,100),
            xaxs="i", yaxs="i" ) )
abline( h=-4:4*10, v=2:10*10, col=gray(0.8) )
matlines( (prCO+prpulse)/2, prCO-prpulse, lwd=c(3,1,1),
          col="blue", lty=1 )
```

But this is not necessary; it is implemented in `plot.MethComp`:

```
plot( ARoxt, pl.type="BA" )
```


pulse =
2.03 + 0.94 CO
(6.01)
CO =
−2.16 + 1.06 pulse
(6.38)
pulse − CO
(CO + pulse) / 2
40
20
0
−20
−40
0
20
40
60
80
100

Implementation in BUGS
Afternoon

Bendix Carstensen

MethComp
28 September 2011
Tutorial, SISMEC, Ancona, Italy

`http://BendixCarstensen.com/MethComp/Ancona.2011`

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.

This is the philosophy in the function `MCmcmc`.

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:

$$\begin{aligned} \alpha_{2|1} &= \alpha_2 - \alpha_1\beta_2/\beta_1 \\ \beta_{2|1} &= \beta_2/\beta_1 \end{aligned}$$

So are the variance components.

Posterior medians used to devise prediction equations with limits.

The MethComp package for R

Implemented model:

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

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

Example output: Oximetry

```
> summary( ox )
        #Replicates
Method     1   2   3 #Items #Obs: 354 Values:  min  med  max
  CO       1   4  56     61       177          22.2 78.6 93.5
  pulse    1   4  56     61       177          24.0 75.0 94.0
>
> MCox  <- MCmcmc( ox, linked=TRUE, n.iter=2000 )
Loading required package: coda
Loading required package: lattice
Loading required package: R2WinBUGS
Loading required package: BRugs
Welcome to BRugs running on OpenBUGS version 3.0.3

Comparison of 2 methods, using 354 measurements
on 61 items, with up to 3 replicate measurements,
(replicate values are in the set: 1 2 3 )
( 2 * 61 * 3 = 366 ):

No. items with measurements on each method:
        #Replicates
Method     1   2   3 #Items #Obs: 354 Values:  min  med  max
  CO       1   4  56     61       177          22.2 78.6 93.5
```

```
Simulation run of a model with
- method by item and item by replicate interaction:
- using 4 chains run for 2000 iterations
  (of which 1000 are burn-in),
- monitoring all values of the chain:
- giving a posterior sample of 4000 observations.

model is syntactically correct
data loaded
model compiled
Initializing chain 1: initial values loaded but this or another
Initializing chain 2: initial values loaded but this or another
Initializing chain 3: initial values loaded but this or another
Initializing chain 4: initial values loaded but this or another
initial values generated, model initialized
Sampling has been started ...
1000 updates took 38 s
deviance set
monitor set for variable 'alpha'
monitor set for variable 'beta'
monitor set for variable 'sigma.mi'
monitor set for variable 'sigma.ir'
monitor set for variable 'sigma.res'
monitor set for variable 'deviance'
```

```
> MCox

 Conversion between methods:
                alpha   beta     sd
To:   From:
CO    CO        0.000  1.000  1.740
      pulse    -9.342  1.159  5.328
pulse CO        8.061  0.863  4.508
      pulse     0.000  1.000  6.115
```

```
 Variance components (sd):
       s.d.
Method    IxR   MxI   res
  CO    3.878 3.122 1.230
  pulse 3.222 2.757 4.324
Variance components with 95 % cred.int.:
    method     CO                  pulse
    qnt       50%   2.5%  97.5%    50%   2.5%  97.5%
SD
IxR         3.878  3.053  4.533  3.222  2.426  3.930
MxI         3.122  2.193  9.764  2.757  1.915  5.902
res         1.230  0.143  2.639  4.324  3.709  5.019
tot         5.220  4.507 10.645  6.135  5.457  7.849
```

```
Mean parameters with 95 % cred.int.:
                      50%    2.5%  97.5% P(>0/1)
alpha[pulse.CO]   8.057  -2.457 29.884   0.969
alpha[CO.pulse] -9.346 -49.949  2.476   0.031
beta[pulse.CO]    0.863   0.604  0.997   0.024
beta[CO.pulse]    1.159   1.003  1.657   0.976
```

Note that intercepts in conversion formulae are adjusted to get conversion formulae that represent the same line both ways, and hence the median interceps in the posterior do not agree exactly with those given in the conversion formulae.

Inter-rater agreement
Afternoon

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28 September 2011
Tutorial, SISMEC, Ancona, Italy

`http://BendixCarstensen.com/MethComp/Ancona.2011`

Program

- Example
- Random rater vs. fixed methods
- Statistical modelling

Example: depression ratings

Patient	Doctor A	B	C	D	E
1	8	9	5	8	8
2	0	0	1	2	1
3	4	5	5	5	3
4	5	8	7	8	5
5	3	3	1	8	2
6	8	9	9	9	1

"Doctor doctor! Am I depressed?"

Getting second opinions ... and third ... and fourth

Example: depression ratings

Research question

How well will two doctors agree on the diagnosis?

In this example we use humans as "measurement methods" or raters.

However, we are not interested in making statements about *specific* raters.

Fixed versus random effects

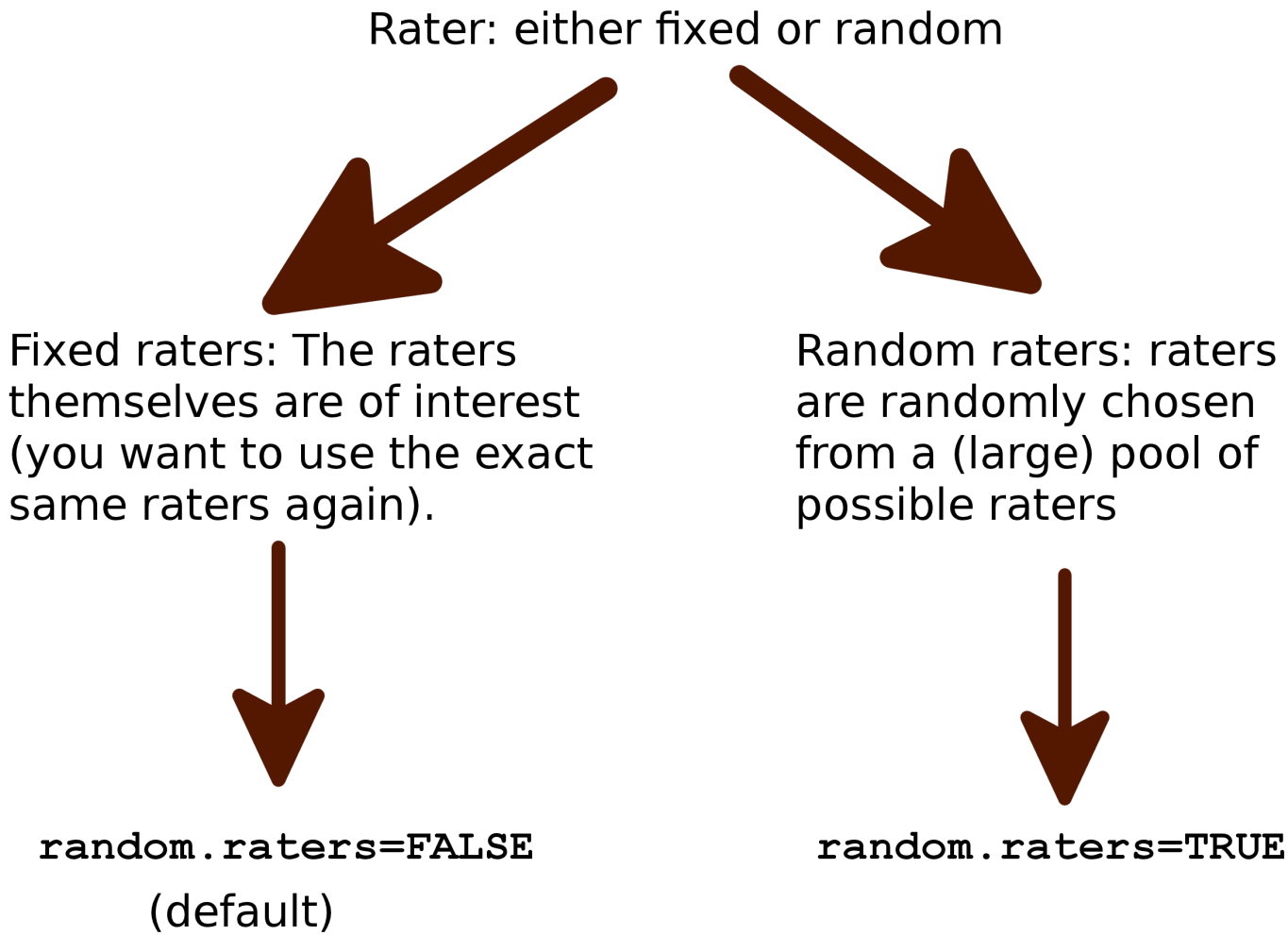
Definition: Factors can either be fixed or random.

- A factor is fixed when the levels (e.g. raters) under study are the only levels of interest.
- A factor is random when the levels under study are a random sample from a larger population of raters and the goal of the study is to make a statement regarding the larger population.

Raters can be defined as fixed or random factors:

- If the raters themselves are of interest (you want to use them again) then use fixed model.
- If raters are randomly chosen of possible pool of raters (you do not have specific raters in mind) then use the random model.

Fixed versus random effects



Modelling: exchangeable replicates

The model for fixed methods is:

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

- Replicates within (m, i) are needed to separate τ and σ.
- Even with replicates, the separate τs are only estimable if $M > 2$.
- Assumes that the difference between methods is constant.
- Assumes *exchangeability* of replicates.

If no replicates then disregard the c_{mi}'s.

Modelling: exchangeable replicates

The model for random methods/raters is:

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

- Replicates within (m, i) are needed to separate τ and σ.
- Even with replicates, the separate τs are only estimable if $M > 2$.
- Note: average difference is 0!
- Assumes *exchangeability* of replicates.

If no replicates then disregard the c_{mi}'s.

Model for replicate measurements

Same approach as before: Fit the correct variance components model and use this as the basis for LoA.

- Extremely flexible.
- Can even be used to analyze the situation where every rater not necessarily has scored every item.

Exchangeable replicates are not uncommon, e.g.,

- Experts scoring/extracting information from images
- Measurements taken on couples/twins.

Linked replicates do not make sense, when it is arbitrary which person is partner 1 or partner 2.

Replicate measurements

The limits of agreement / prediction interval for two random raters scoring a new future observation is

$$0 \pm 1.96 \sqrt{\underbrace{2\xi^2}_{\text{Extra variation}} + \tau_1^2 + \tau_2^2 + \sigma_1^2 + \sigma_2^2}$$

However, since we are considering the prediction interval for two *random* raters we use the average variance components in the formula

$$0 \pm 1.96 \sqrt{2(\xi^2 + \bar{\tau^2} + \bar{\sigma^2})}$$

Note that the expected difference is zero since we have no fixed order of the raters.

Example: Stress scoring of dogs

10 judges scoring stress indicators from 10 dogs.

```
> dogdata <- Meth(item=1, y=2:11, data=dogs)
> BA.est(dogdata, random.raters=TRUE, linked=FALSE)

 Variance components (sd):
    IxR    MxI     M    res
j1    0 18.145 14.11 20.948
j10   0  8.122 14.11 12.736
j2    0  0.009 14.11 11.350
j3    0  0.004 14.11  9.524
j4    0  0.004 14.11  9.614
j5    0  8.924 14.11 12.588
j6    0 18.534 14.11 21.135
j7    0  0.023 14.11 11.991
j8    0  0.004 14.11  9.384
j9    0  0.003 14.11  9.789
```

Example: Stress scoring of dogs

10 judges scoring stress indicators from 10 dogs.

```
> res <- BA.est(dogdata, random.raters=TRUE,
+                 linked=FALSE)
> res$LoA
                      Mean     Lower    Upper       SD
Rand. rater - rater      0 -61.02451 61.02451 30.51225
```

Linked replicates

For linked replicates, extend the model as before:

$$
\begin{aligned}
y_{mir} &= b_m + \mu_i + a_{ir} + c_{mi} + e_{mir} \\
&\quad \text{s.d.}(b_m) = \xi \quad \text{— variation among raters} \\
&\quad \text{s.d.}(a_{ir}) = \omega \quad \text{— between replicates} \\
&\quad \text{s.d.}(c_{mi}) = \tau_m \quad \text{— “matrix”-effect} \\
&\quad \text{s.d.}(e_{mir}) = \sigma_m \quad \text{— measurement error}
\end{aligned}
$$

The variation between replicates, ω, does not enter the limits-of-agreement since the LoA's are for a single new future observation (ie., the same replicate from one item/individual for both raters).

$$0 \pm 1.96\sqrt{2(\xi^2 + \bar{\tau^2} + \bar{\sigma^2})}$$

Linked replicates

```
> dogdata <- Meth(item=1, y=2:11, data=dogs)
> BA.est(dogdata, random.raters=TRUE)

 Variance components (sd):
      IxR    MxI      M    res
j1  6.466 18.754 13.994 21.672
j10 6.466  8.163 13.994 10.454
j2  6.466  3.213 13.994 10.439
j3  6.466  0.011 13.994  5.718
j4  6.466  0.033 13.994 11.716
j5  6.466  8.817 13.994 10.449
j6  6.466 19.205 13.994 21.770
j7  6.466  4.732 13.994 10.523
j8  6.466  0.009 13.994  5.701
j9  6.466  0.026 13.994 11.441
```

Linked replicates

```
> res2 <- BA.est(dogdata, random.raters=TRUE)
> res2$LoA

                       Mean      Lower    Upper       SD
Rand. rater - rater       0 -60.47317 60.47317 30.23658
```

Random raters

- Fit the correct variance component model where variation among raters is considered a random effect
- Since each rater can have his/her individual variance we need to average the individual variance components
- Extract the relevant variance components and compute the limits-of-agreement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