Analysis of Method Comparison Studies

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Comparing two methods with one measurement on each

Thursday 19 February

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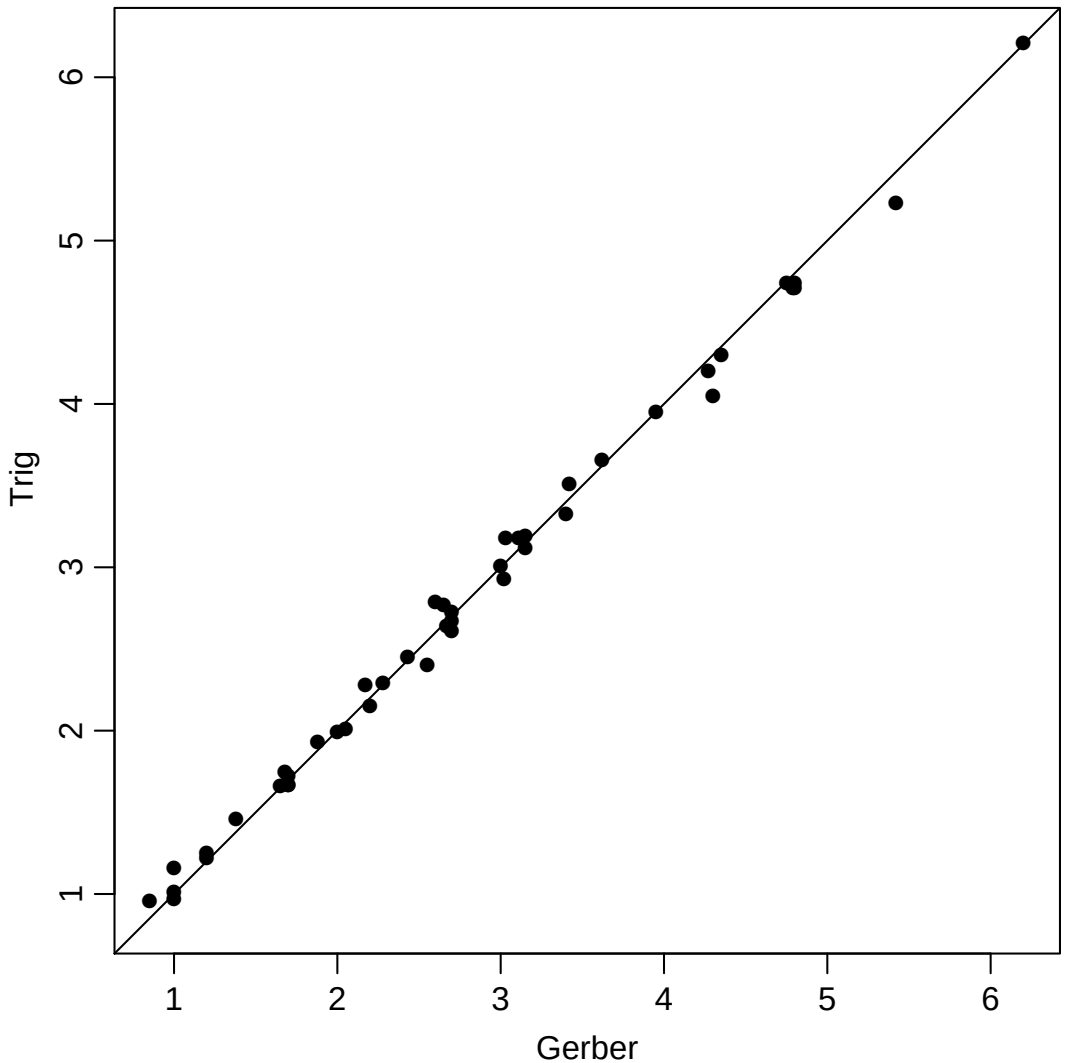
(Comp-simple)

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?

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

"Limits of agreement:"

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

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

Limits of agreement: Interpretation

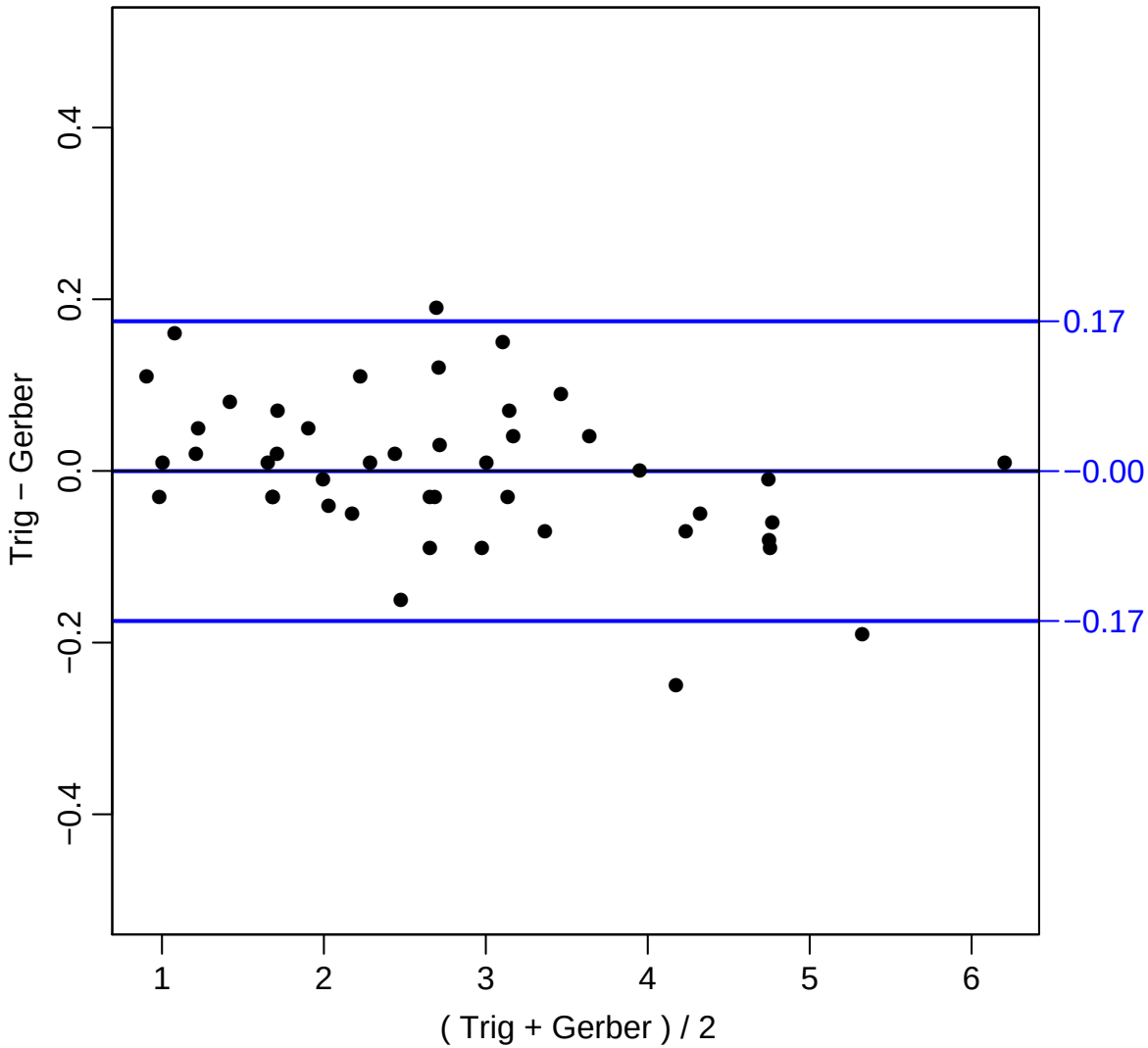
- If a new patient is measured **once** with each of the two methods, the difference between the two values will with 95% probability be within the limits of agreement.
- This is a **prediction** interval for a (future) difference.
- Requires a **clinical** input:
  Are the limits of agreement sufficiently 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.
- It is an **equivalence** problem:
  1: Testing is irrelevant.
  2: Clinical input is required.

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:

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

But it can of course also be converted to a prediction interval for y_2 given y_1:

$$\hat{y}_{2|1} = \hat{y}_2|y_1 = \alpha_2 - \alpha_1 + y_1 \pm 1.96\,\mathrm{s.d.}(D)$$

Spurious correlation?

Unequal variances induce correlation between D_i and A_i; if variances of y_{1i} and y_{2i} are ζ_1^2 and ζ_2^2 respctively:

$$\text{cov}(D_i, A_i) = \frac{1}{2}(\zeta_1^2 - \zeta_2^2) \neq 0 \quad \text{if } \zeta_1 \neq \zeta_2$$

In correlation terms:

$$\rho(D, A) = \frac{1}{2}\frac{\zeta_1^2 - \zeta_2^2}{\zeta_1^2 + \zeta_2^2}$$

i.e. the correlation depends on whether the difference between the variances is large relative to the sizes of the two.

— not really

The variances we were using were the *marginal* variances of y_1 and y_2:

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

so we have that the marginal variances are:

$$\mathrm{var}(y_m) = \mathrm{var}(\mu_i) + \sigma_m^2$$

and hence the correlation expression is:

$$\rho(D, A) = \frac{1}{2}\frac{\zeta_1^2 - \zeta_2^2}{\zeta_1^2 + \zeta_2^2} = \frac{1}{2}\frac{\sigma_1^2 - \sigma_2^2}{2\mathrm{var}(\mu_i) + \sigma_1^2 + \sigma_2^2}$$

Hence only relevant if $\mathrm{var}(\mu_i)$ is small relative to σ_1^2 and σ_2^2. **Not** likely in practise.

Introduction to computing

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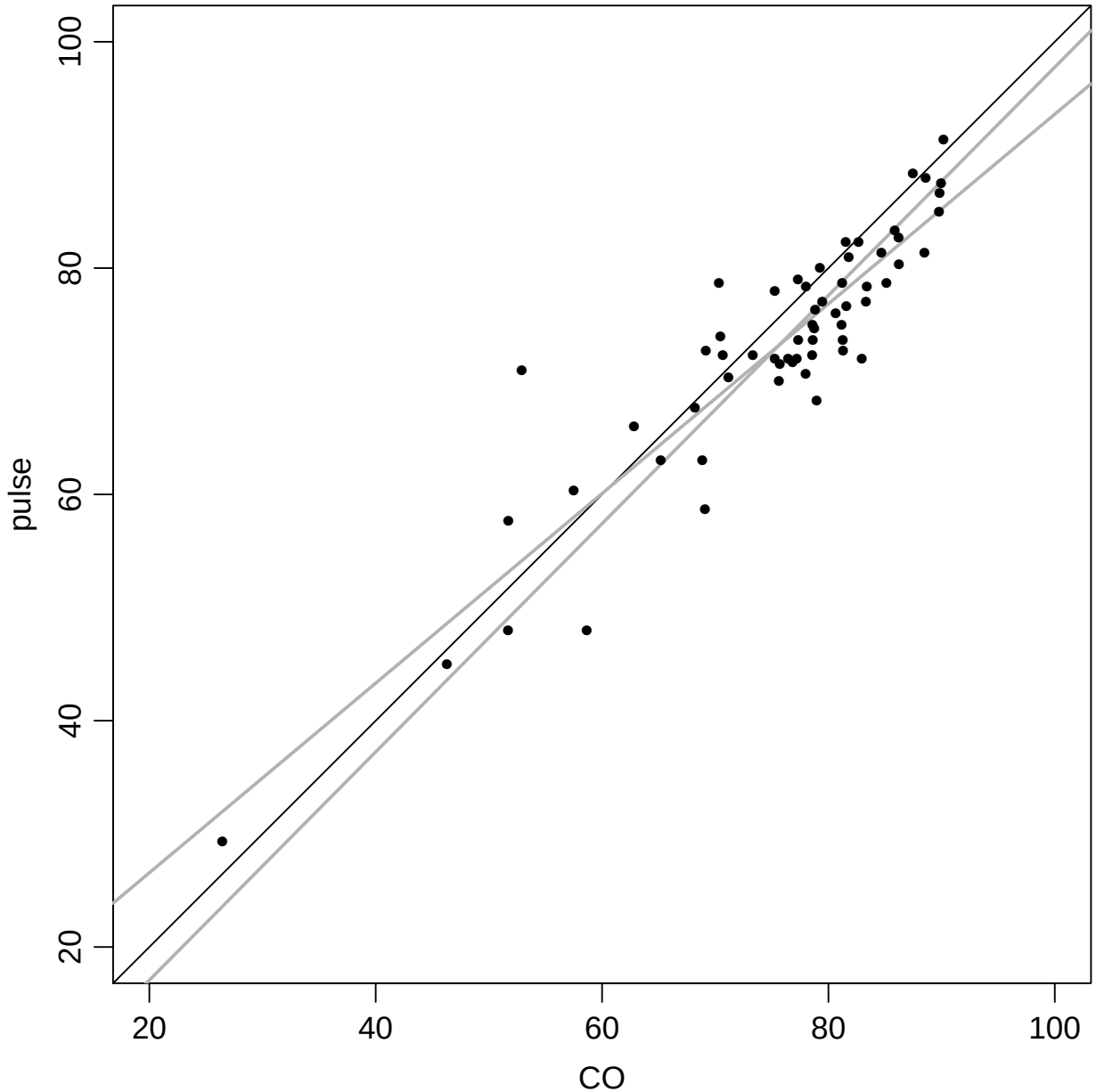
(Intro-comp)

Course structure

The course 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.

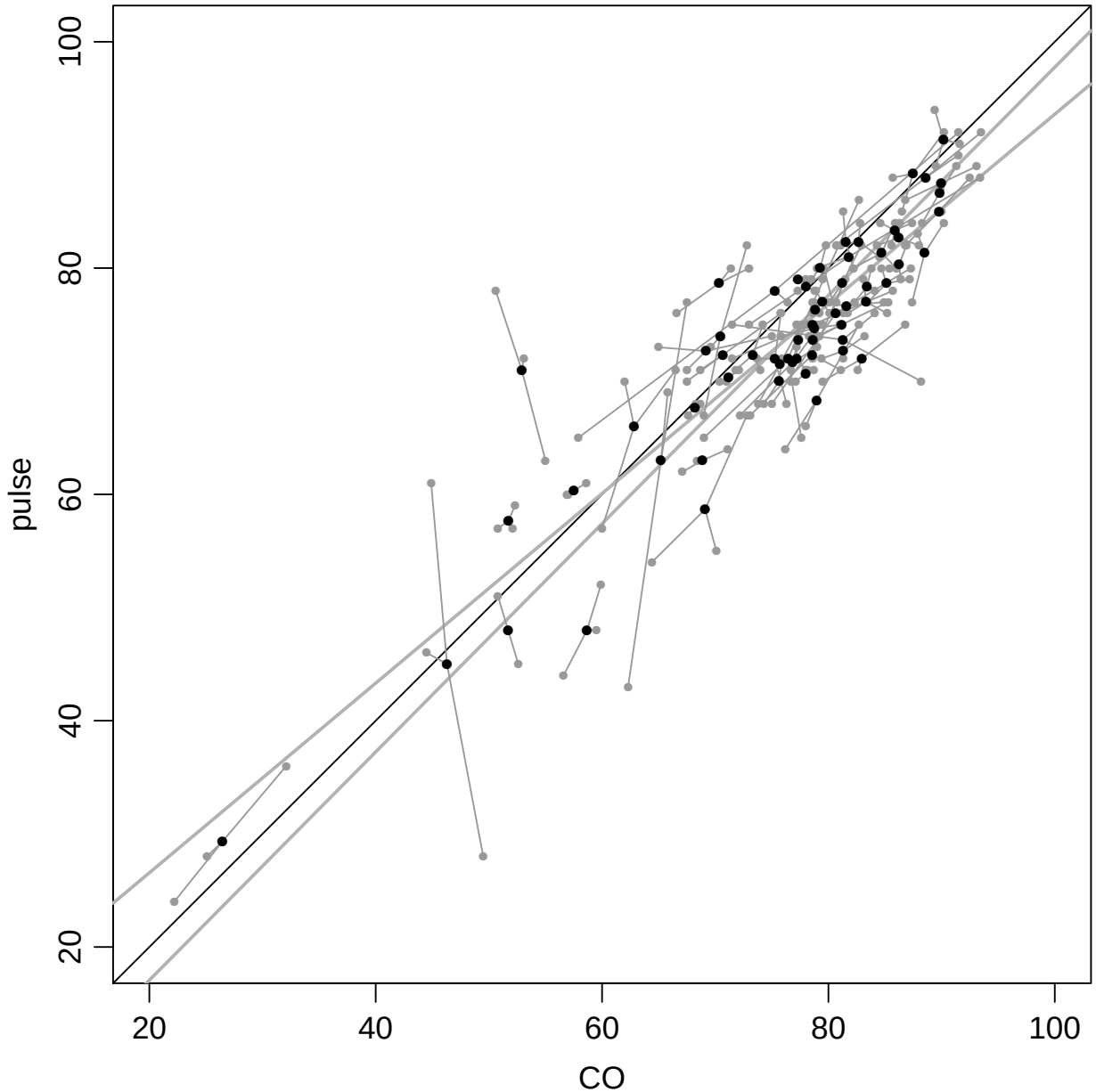
- **R** for data manipulation and graphics.
- Occasionally `BUGS` for estimation in non-linear variance component models.

Oximetry data



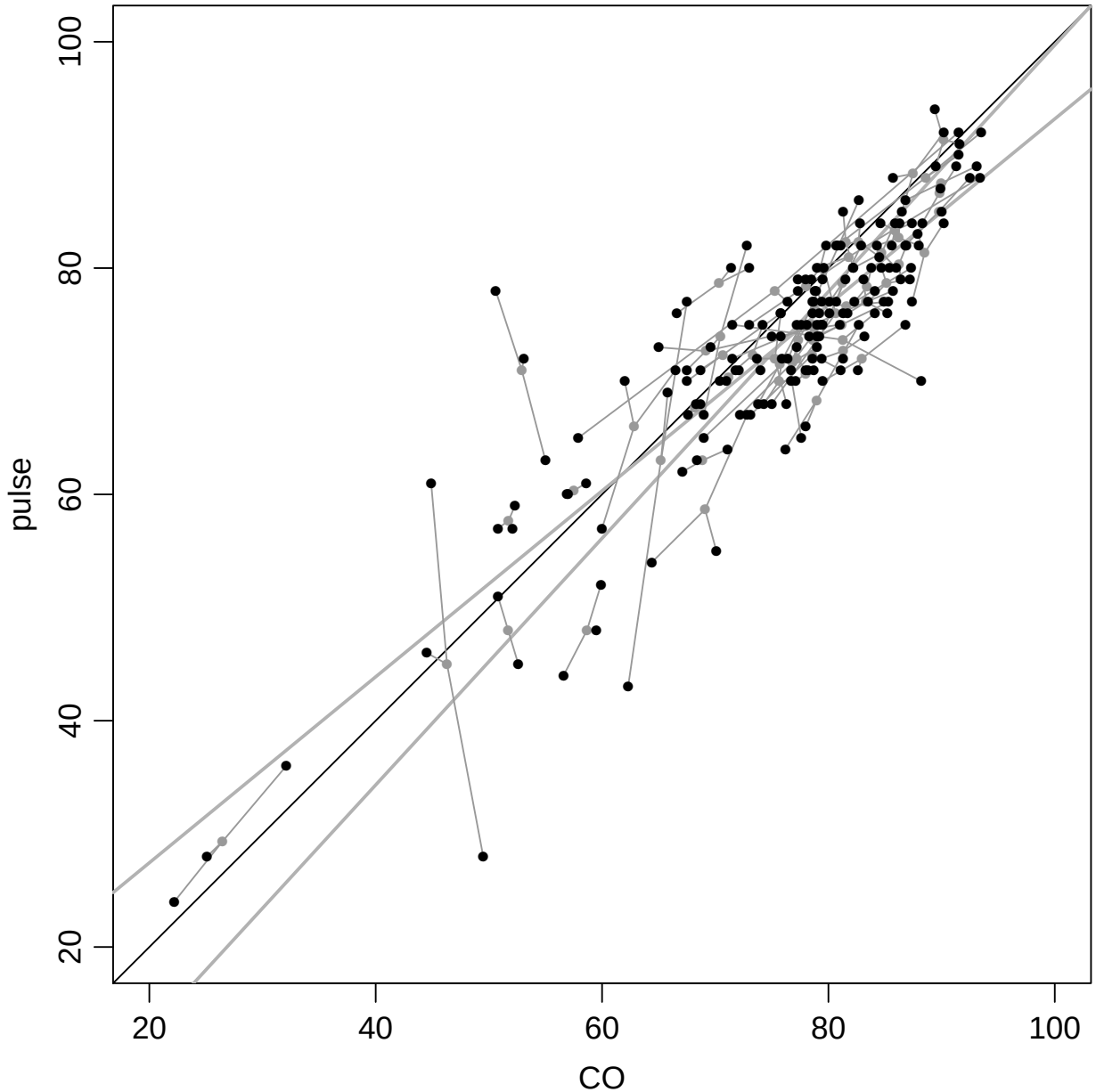
Means over replicates.

Oximetry data



Linked replicates.

Oximetry data



Linked replicates.

How it works

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

The function 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
```

Analyses in this course

- Scatter plots.
- Bland-Altman plots ($y - x$ vs. $(x + y)/2$)
- Limits of agreement.
- Models with constant bias.
- Models with linear bias.
- Conversion formulae between methods (single replicates)
- Plots of converison equations.
- Reporting of variance components.

Requirements

- **R** for data manipulation and graphics:
- `Tinn-R` convenience editor with syntax highlighting for **R**. Alternatively you can use the bulit-in editor in **R**, or the nerds can use `ESS`.
- `nlme`-package for variance component models — constant bias.
- `BUGS` for fitting models with linear bias (non-linear variance component models, over-parametrized).

All of it works from within **R**.

Functions in the `MethComp` package

5 broad categories of functions in `MethComp`:

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

Graphical functions (basic)

- `BA.plot` Makes a Bland-Altman plot of two methods from a data frame with method comparison data, and computes limits of agreement. The plotting etc is really done by a call to
- `BlandAltman` Draws a Bland-Altman plot and computes limits of agreement.
- `plot.Meth` Plots all methods against all other, both as a scatter plot and as a Bland-Altman plot.
- `bothlines` Adds regression lines of y on x and vice versa to a scatter plot.

Data manipulation functions

- `make.repl` Generates a `repl` column in a data frame with columns `meth`, `item` and `y`.
- `perm.repl` Randomly permutes replicates within (method,item) and assigns new replicate numbers.
- `to.wide`/`to.long` Transforms a data frame in the long form to the wide form and vice versa.
- `Meth.sim` Simulates a dataset (a `Meth` object) from a method comparison experiment.

Analysis functions (simple)

- `Deming` Performs Deming regression, i.e. regression with errors in both variables.
- `BA.est` Estimates in the variance components models underlying the concept of limits of agreement, and returns the bias and the variance components as well as limits of agreent and preproducibility. Assumes constant bias between methods.
- `VC.est` The workhorse behind `BA.est`.
- `DA.reg`, regresses the differences on the averages, and derives the corresponding conversion equations. Also regresses the absolute residuals on the averages to check whether the variance is constant across the

Analysis functions (general)

- `AltReg` Estimates via ad-hoc procedure (alternating regressions) in a model with linear bias between methods. Returns a matrix of estimates both for the mean conversion and for the variance components.
- `MCmcmc` Estimates via `BUGS` in the general model with non-constant bias (and in the future) possibly non-constant standard deviations of the variance components. Produces a `MCmcmc` object.

Reporting functions

- `summary.Meth` Tabulates replicates by methods and items.
- `print.MCmcmc` Prints a table of conversion equation between methods analyzed, with prediction standard deviations. Also gives summaries of the posteriors for the parameters that constitute the conversion algorithms.
- `plot.MCmcmc` Plots the conversion lines between methods with prediction limits.
- `post.MCmcmc` Plots smoothed posterior densities for the variance component estimates.
- `trace.MCmcmc` Plots the simulation traces from an `MCmcmc` object.

Does it work?

You should get something reasonable out of this:

```
library(MethComp)
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)
print(MC.ox)
plot(MC.ox)
trace.MCmcmc(MC.ox)
post.MCmcmc(MC.ox)
```

Non-constant difference

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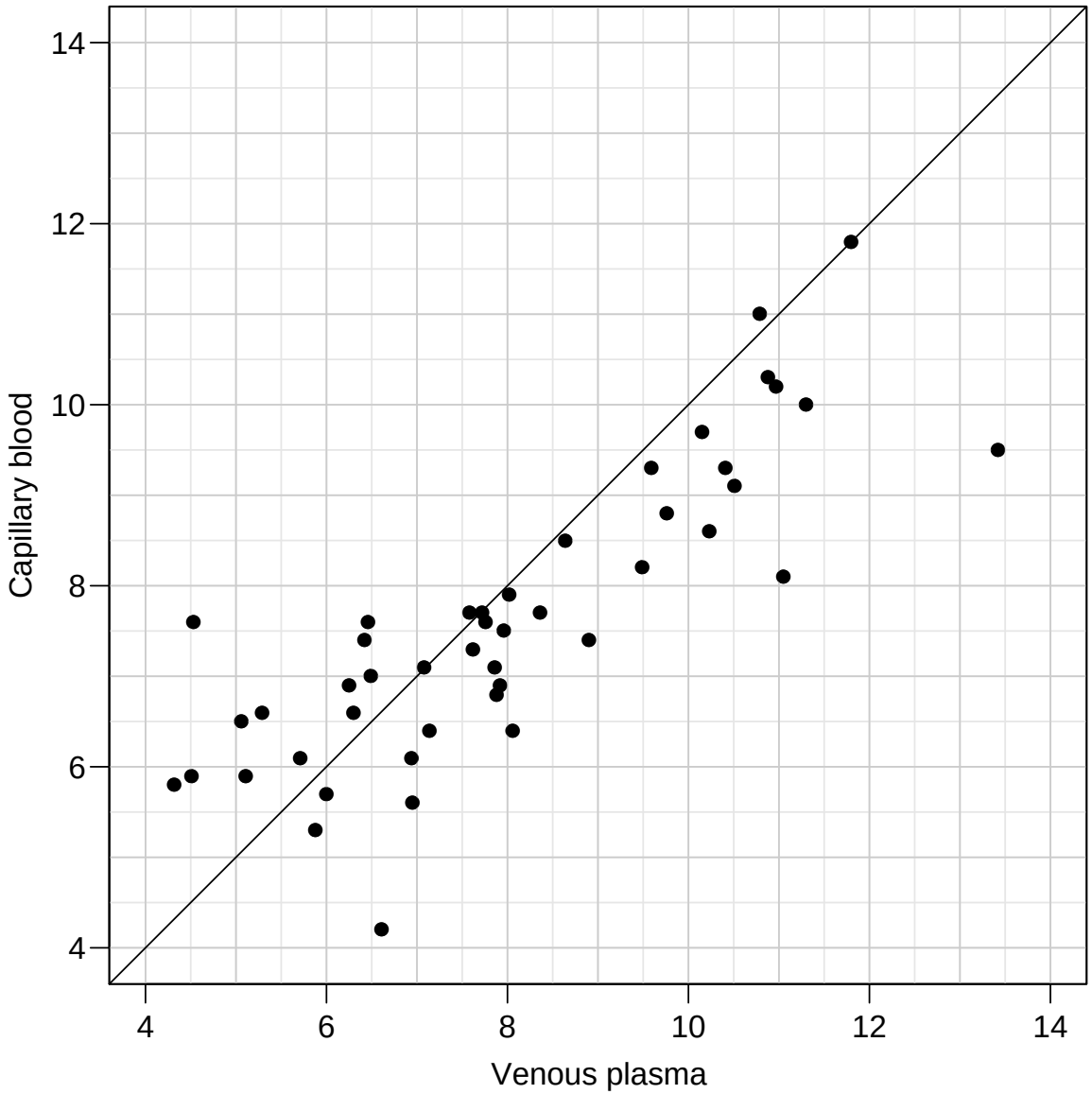
Limits of agreement — assumptions

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

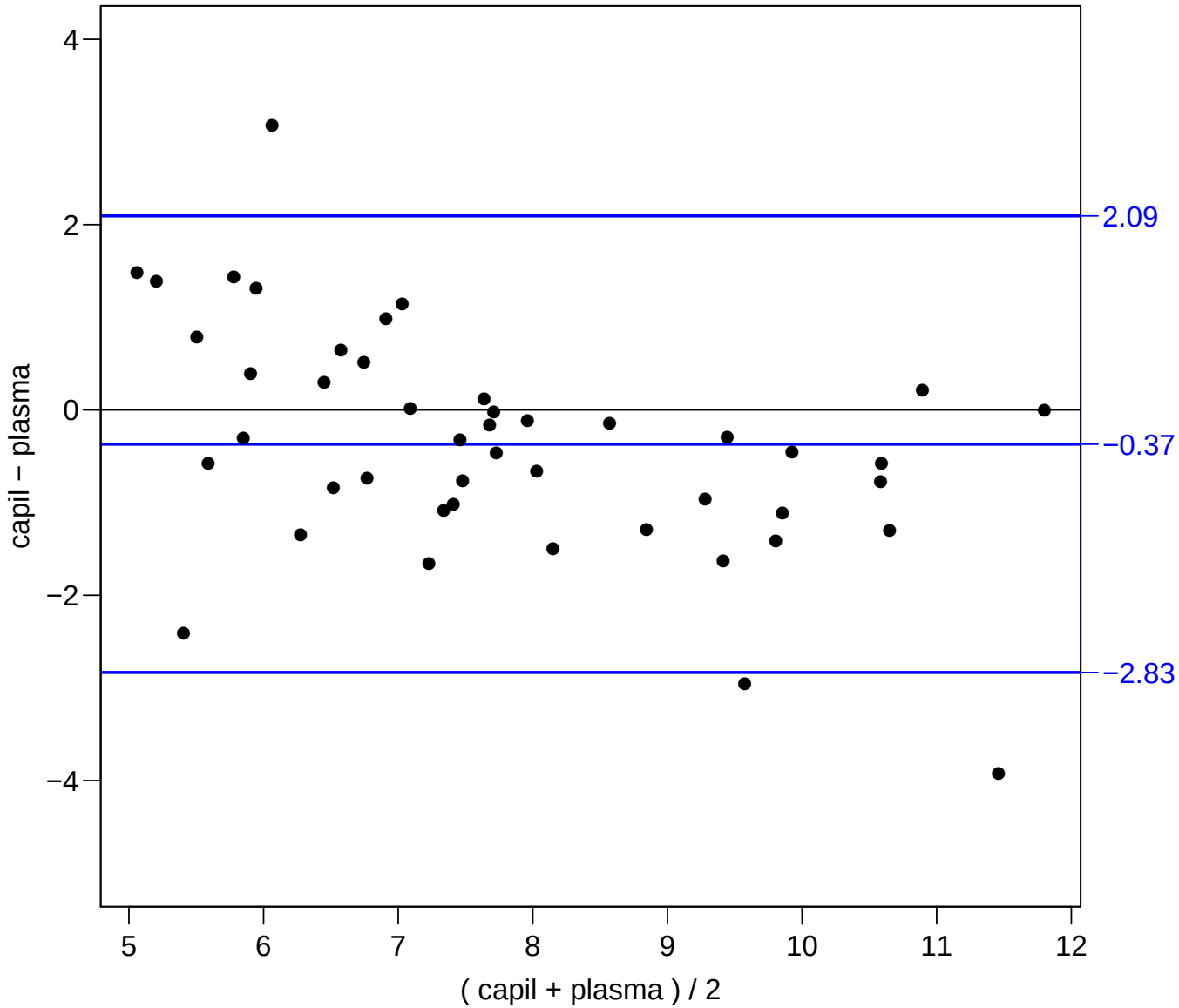
Check this by:

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

Glucose measurements



Glucose measurements



Regress difference on avarage

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

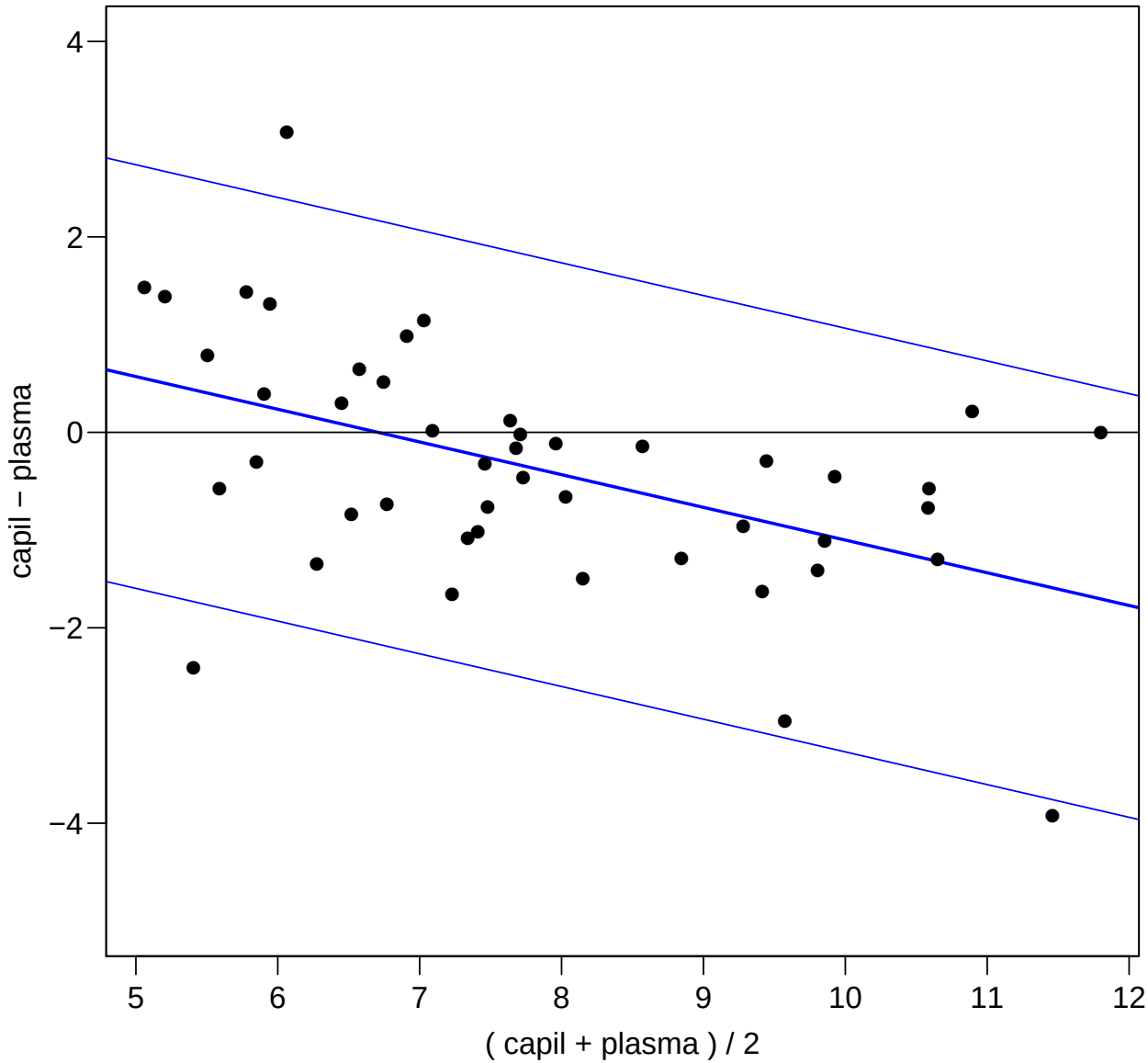
If b is different from 0, we could use this equation to derive LoA:

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

or convert to prediction as for LoA:

$$y_1 = y_2 + a + bA_i \approx y_2 + a + by_2 = a + (1 + b)y_2$$

Variable limits of agreement



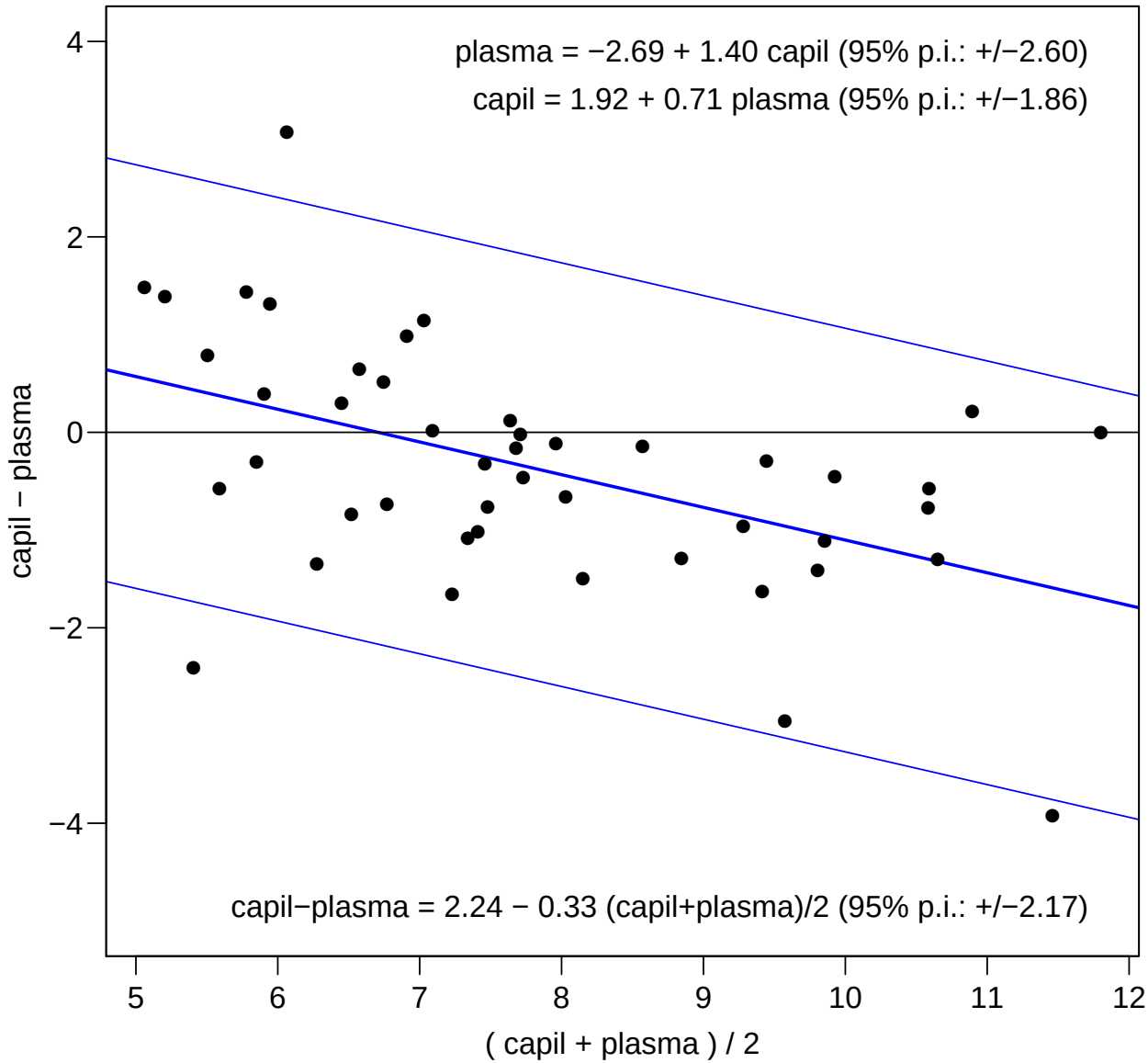
Regress difference on average

We can do better:

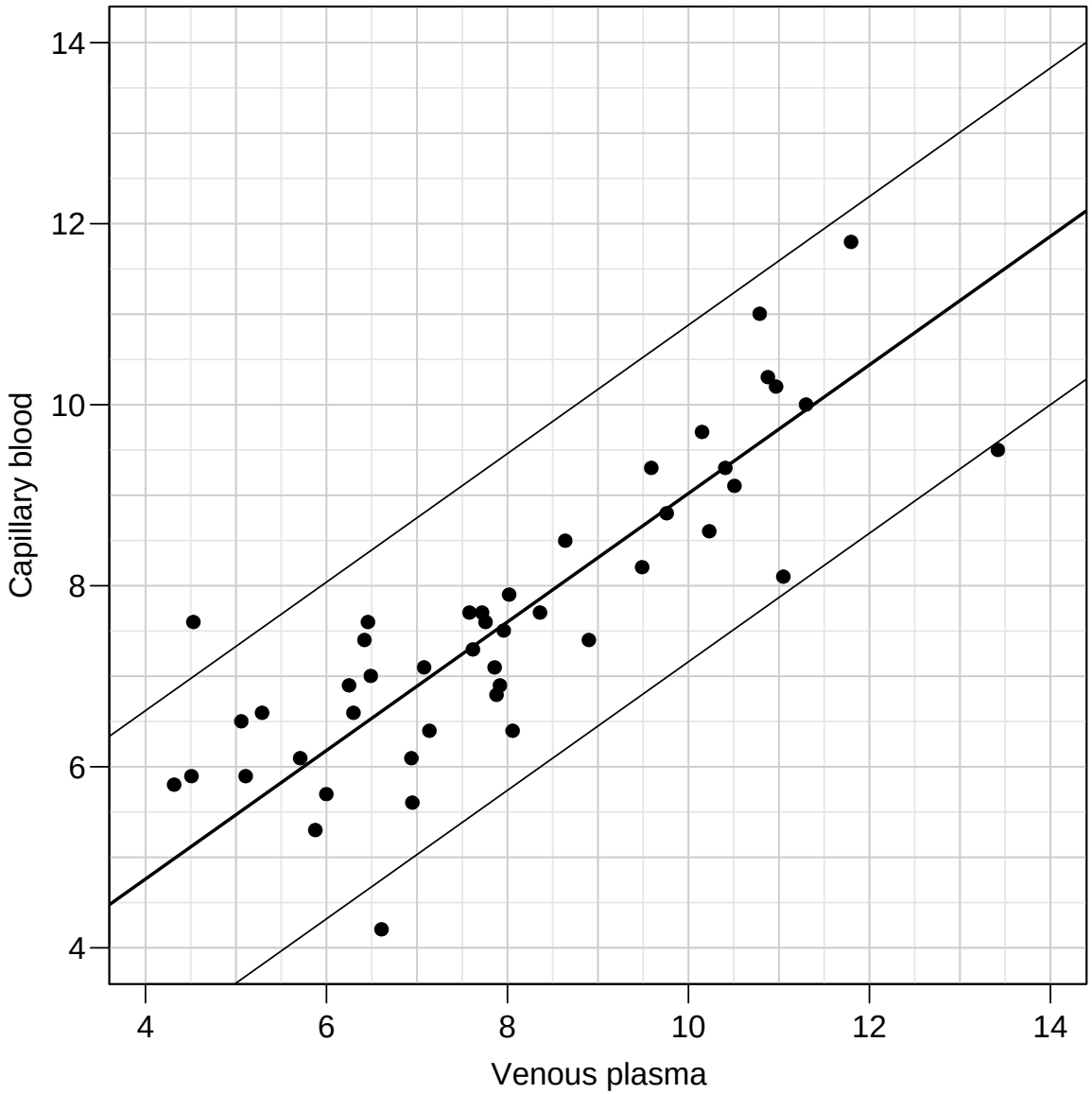
$$
\begin{aligned}
y_{1i} - y_{2i} &= a + b(y_{1i} + y_{2i})/2 + e_i \\
y_{1i}(1 - b/2) &= a + (1 + b/2)y_{2i} + e_i \\
y_{1i} &= \frac{a}{1 - b/2} + \frac{1 + b/2}{1 - b/2} y_{2i} + \frac{1}{1 - b/2} e_i \\
y_{2i} &= \frac{-a}{1 + b/2} + \frac{1 - b/2}{1 + b/2} y_{1i} + \frac{1}{1 + b/2} e_i
\end{aligned}
$$

This is what comes out of `DA.reg` and `BA.plot(glu120,reg.line=2)`

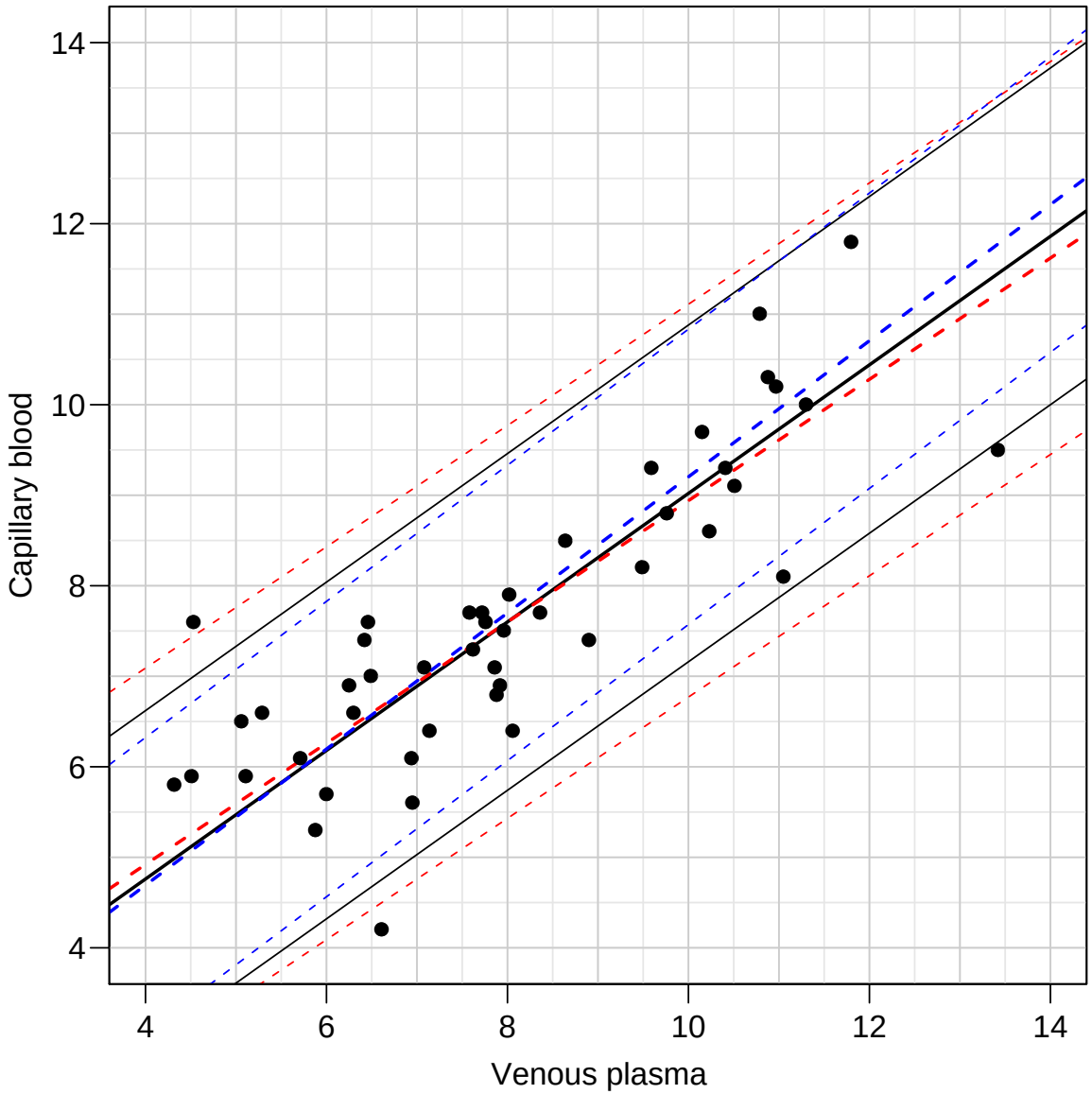
Variable limits of agreement



Conversion equation with prediction limits



Conversion equation with prediction limits



Why does this work?

The general model for the data is:

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

- 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.

So why is it wrong anyway?

Conceptually:

Once the β_m is introduced:

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

measurements by different methods are on different scales.

Hence it has no mening to form the differences.

So why is it wrong anyway?

Statistically:

Under the correctly specified model, the induced model for the differences on the averages A_i, these contain the error terms, and so does the residuals.

So the covariate is not independent of the error terms.

Thus the assumptions behind regression are violated.

Then why use it?

- With only one observation per (method,item) there is not much else to do.
- If the slope linking the two methods (β_1/β_2) is not dramatically different from 1, the violatiosn are not that big.
- Implemented in `BA.plot` and in `DA.reg`, which also checks the residuals.

For further details, see [3].

Comparing two methods with replicate measurements

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(comp-repl)

Extension of the model: replicate measurements

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

- Replicates within (m, i) 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.
- Assumes *exchangeability* of replicates.

Extension of the model: replicate measurements

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

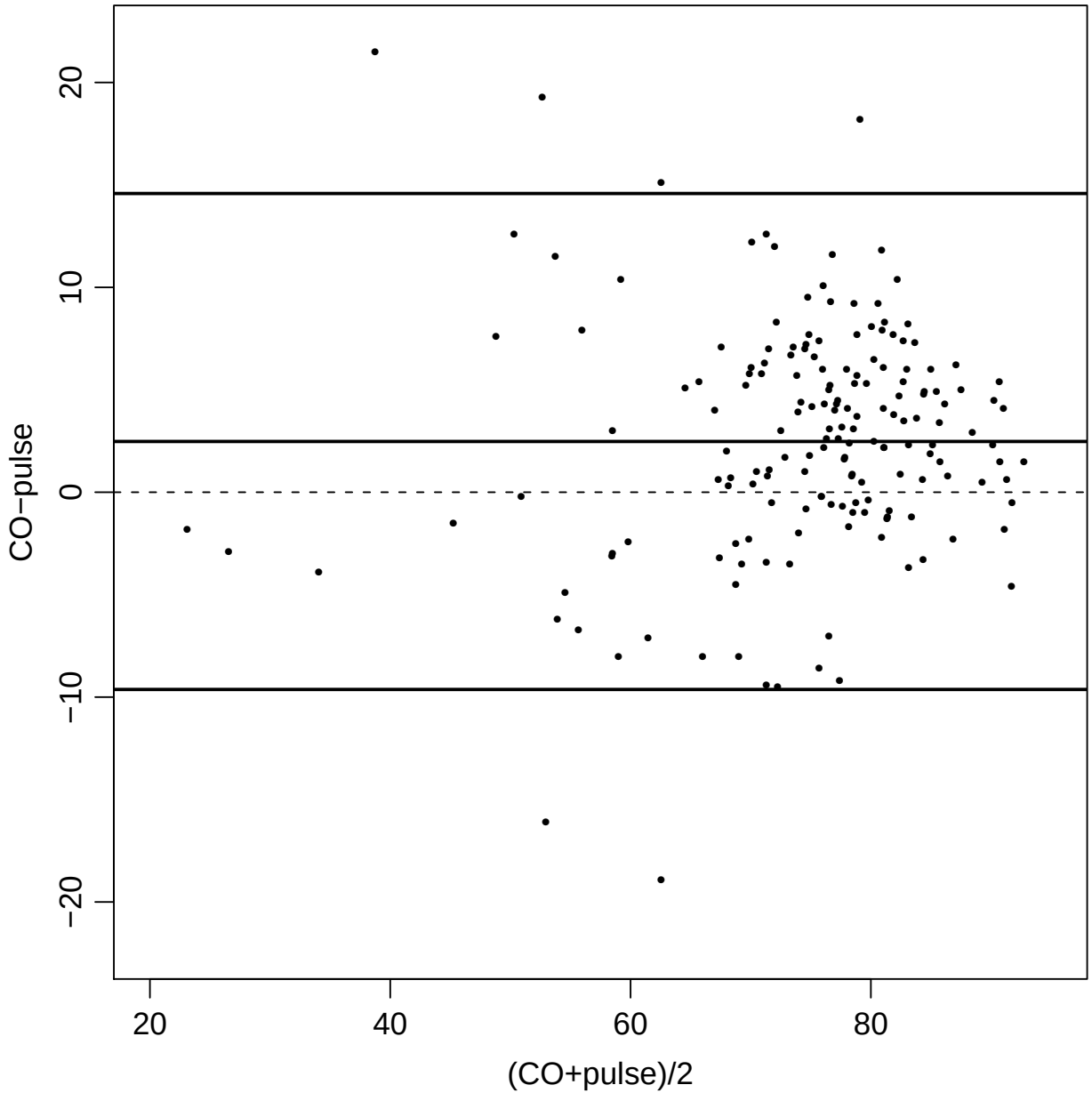
- Still assumes that the difference between methods is constant.
- Replicates are *linked* between methods: a_{ir} is common across methods, i.e. the first replicate on a person is made under similar conditions for all methods (i.e. at a specific day or the like).

Replicate measurements

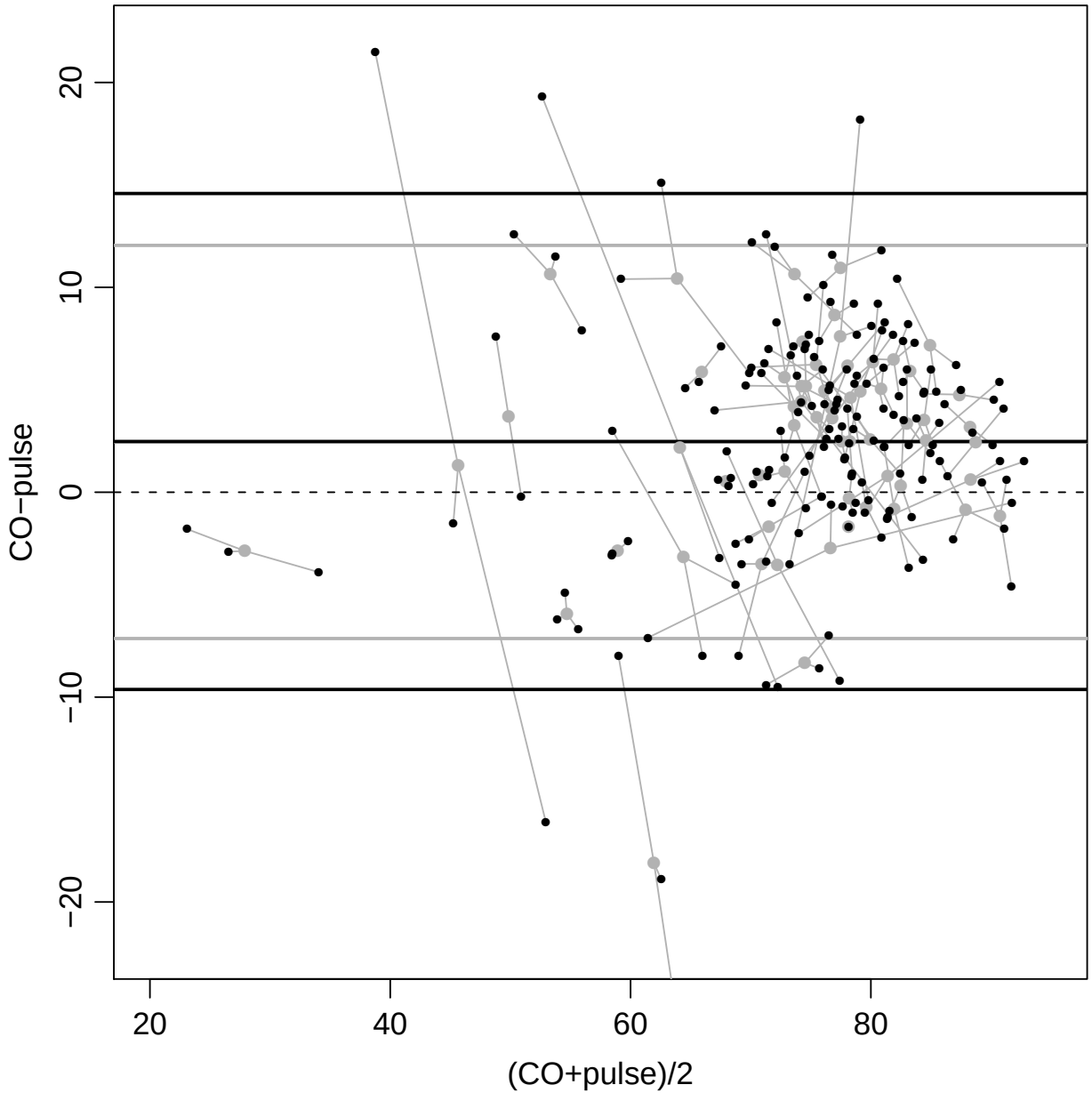
Three approaches to limits of agreement with replicate measurements:

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)` — next lecture.

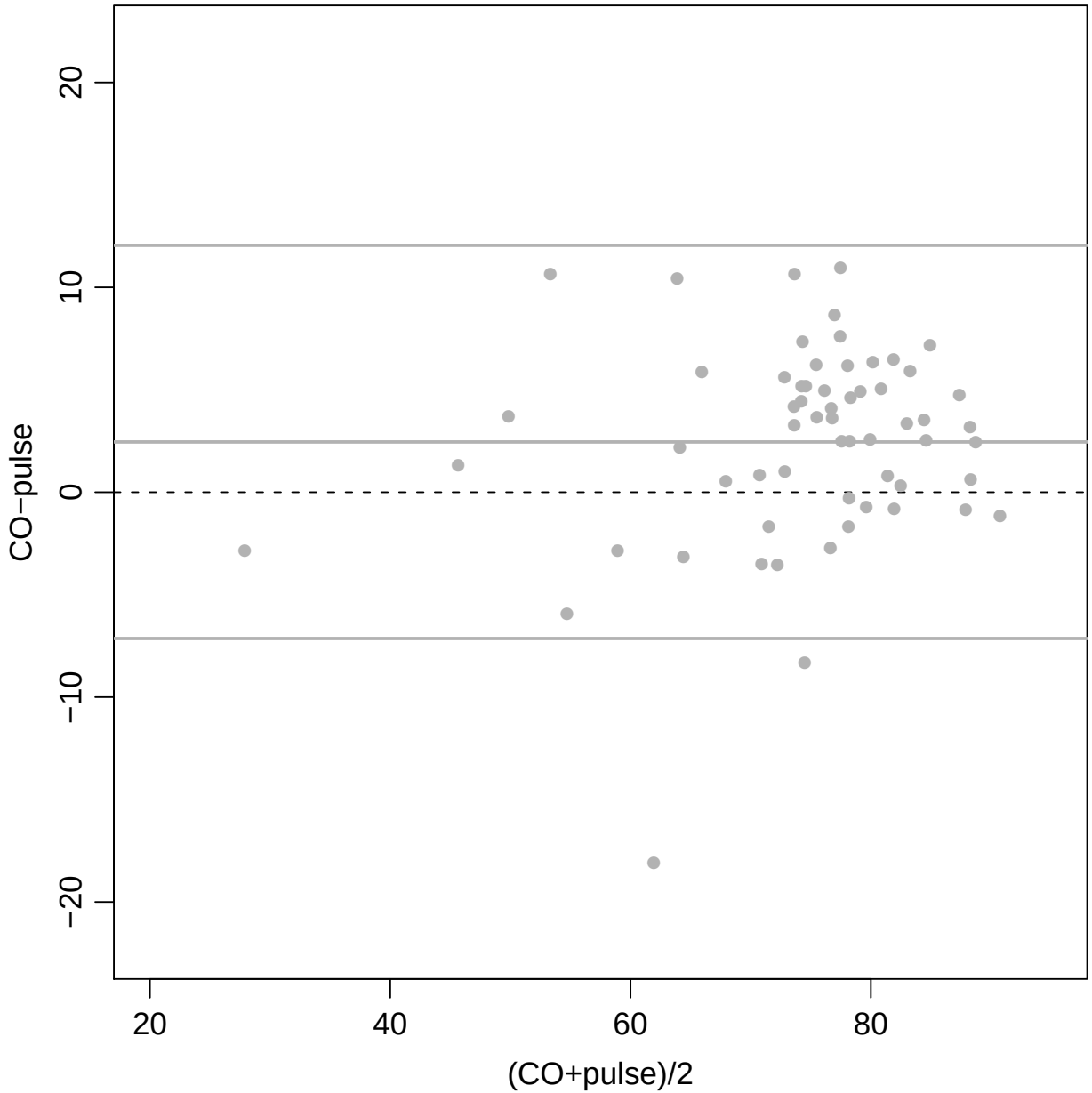
Oximetry data



Oximetry data



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:

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

If we are using 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:

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

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

Exchangeable replicates as items?

If replicates are exchangeable it is not clear how to produce the differences using replicates as items.

If replicates are paired at random (se the function `perm.repl`), the variance will still be correct using the model without the $i \times r$ interaction term (a_{ir}):

$$\text{var}(y_{1ir} - y_{2is}) = \tau_1^2 + \sigma_1^2 + \tau_2^2 + \sigma_2^2$$

Differences will be positively correlated within item:

$$\text{cov}(y_{1ir} - y_{2is}, y_{1it} - y_{2iu}) = \tau_1^2 + \tau_2^2$$

— slight underestimate of the true variance.

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.

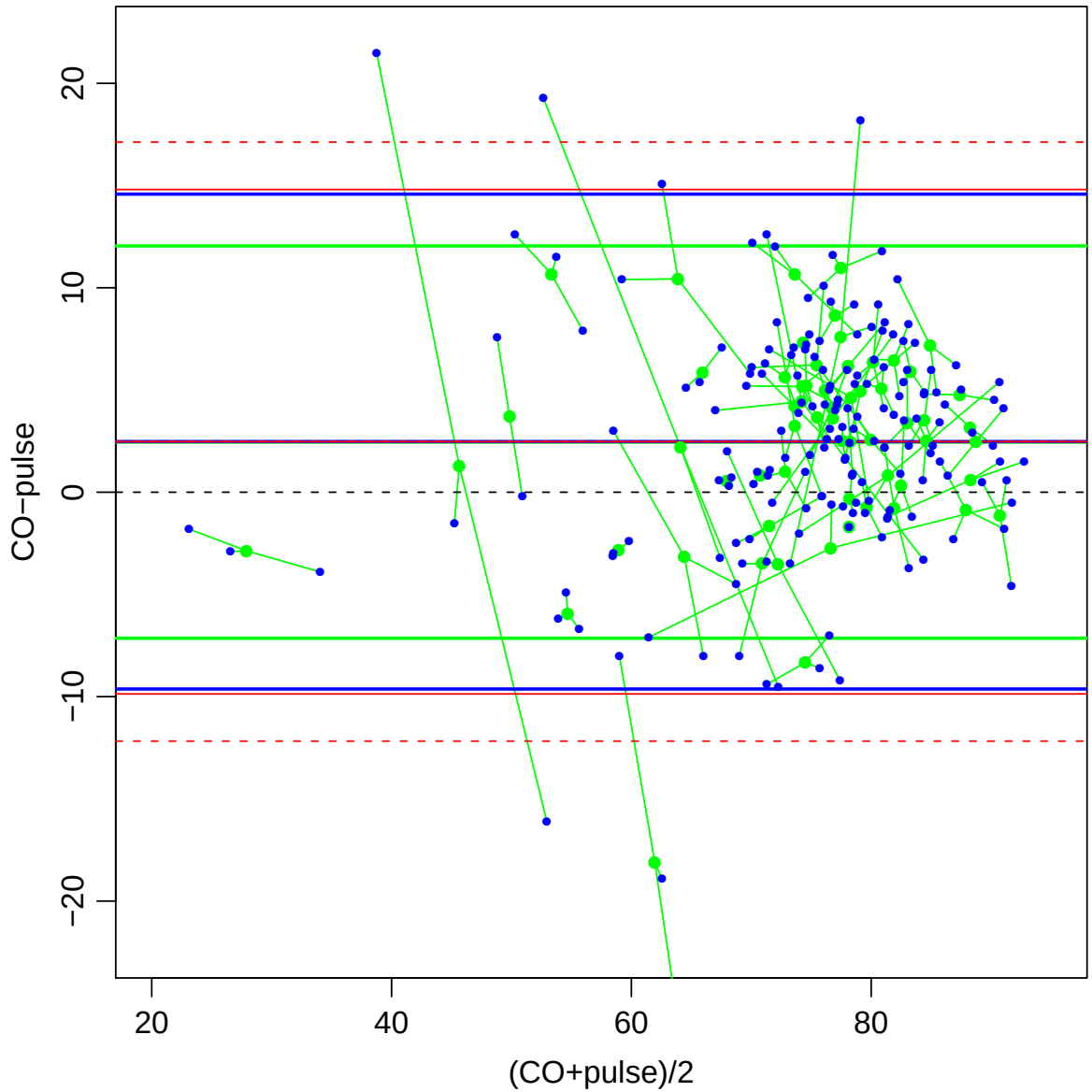
Further details, see [4].

Oximetry data

Linked replicates used as items

Mean over replicates as items

Limits based on model — dashed line assuming exchangeable replicates



Repeatability and reproducibility

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(Repro)

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.

A general model

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(General)

Extension of the model:

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

Method, Item, Replicate

- 1 3-way interaction
- 3 2-way interactions

What part of the interactions should be systematic (fixed) and what part should be random?

(m, r) - between replicates within method

This effect has $M \times R$ levels, usually a rather small number.

This effect will therefore normally be modelled as a fixed effect, but not necessarily with $M \times R$ parameters, presumably fewer.

If replicates are times of sampling or analysis, we may consider different time trends for each method, e.g.

$$d_{mr} = \gamma_m t_r$$

A random $m \times r$-effect would be hard to interpret. Omitted in the rest of this.

(i, r) - between replicates within individual

Observations with same (i, r) — but different method — will be correlated.

Use if all methods are applied to each item at

- different times
- at different locations
- at different conditions

This means there is a minimal structure to replicates — they are linked.

There might be further structure, e.g. a systematic effect of a time.

(m, i) - between methods within individual

This is what is often called a "matrix" effect.

Matrix in the chemical sense: The surrounding matter ("matrix") in which the substance of interest is dissolved.

Represents random effects of items reacting differently on each measurement method.

Logical to require that the variance of these methods was allowed to differ between methods.

Variance component model!

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

Note we do not consider the method by replicate interaction any more.

The model is a (standard) variance component model, where two of the variance components depend on method.

Fitting the variance component model

Complicated and counter-intuitive in **R**:

```
> library( nlme )
> lme( y ~ meth + item,
       random = list( item = pdIdent(~meth - 1),
                      repl = ~1),
       weights = varIdent(form = ~1 | meth),
       data = ox)
```

Packed solution

This model has been packaged in a function that calls `lme` and then tease out the relevant parameters.

```
> BA.est(ox,linked=TRUE)
$Bias
       CO     pulse
 0.000000 -2.470446

$VarComp
             IxR      MxI      res
CO    3.415692 2.928042 2.224868
pulse 3.415692 2.928042 3.994451

$LoA
                    Mean     Lower    Upper       SD
pulse - CO   -2.470446 -14.80779 9.866901 6.168674

$RepCoef
             SD    Coef.
CO    5.764892 11.52978
pulse 7.432710 14.86542
```

Linear bias between methods

Thursday 19 February

Bendix Carstensen

Analysis of Method Comparison Studies
18 February 2009
University of Adelaide

(Lin-bias)

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*.

Variance components

Method, Item, Replicate.

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

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

If only two methods compared:
τ_1 and τ_2 cannot be separated. Variances must be reported on the scale of each method, as $\beta_m \tau_m$.

Variance components

Method, Item, Replicate.

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

Common across methods — must be scaled relative to the methods.

Included if replicates are linked across methods, e.g. if there is a sequence in the replicates.

The relevant quantities to reports are $\beta_m\omega$ — the s.d. on the scale of the mth method.

Converting between methods

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(Convert)

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:

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

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

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

The width of the prediction interval is:

$$
2 \times 1.96 \times \sqrt{\left(\frac{\beta_2}{\beta_1}\right)^2(\beta_1^2\tau_1^2 + \sigma_1^2) + (\beta_2^2\tau_2^2 + \sigma_2^2)}
$$

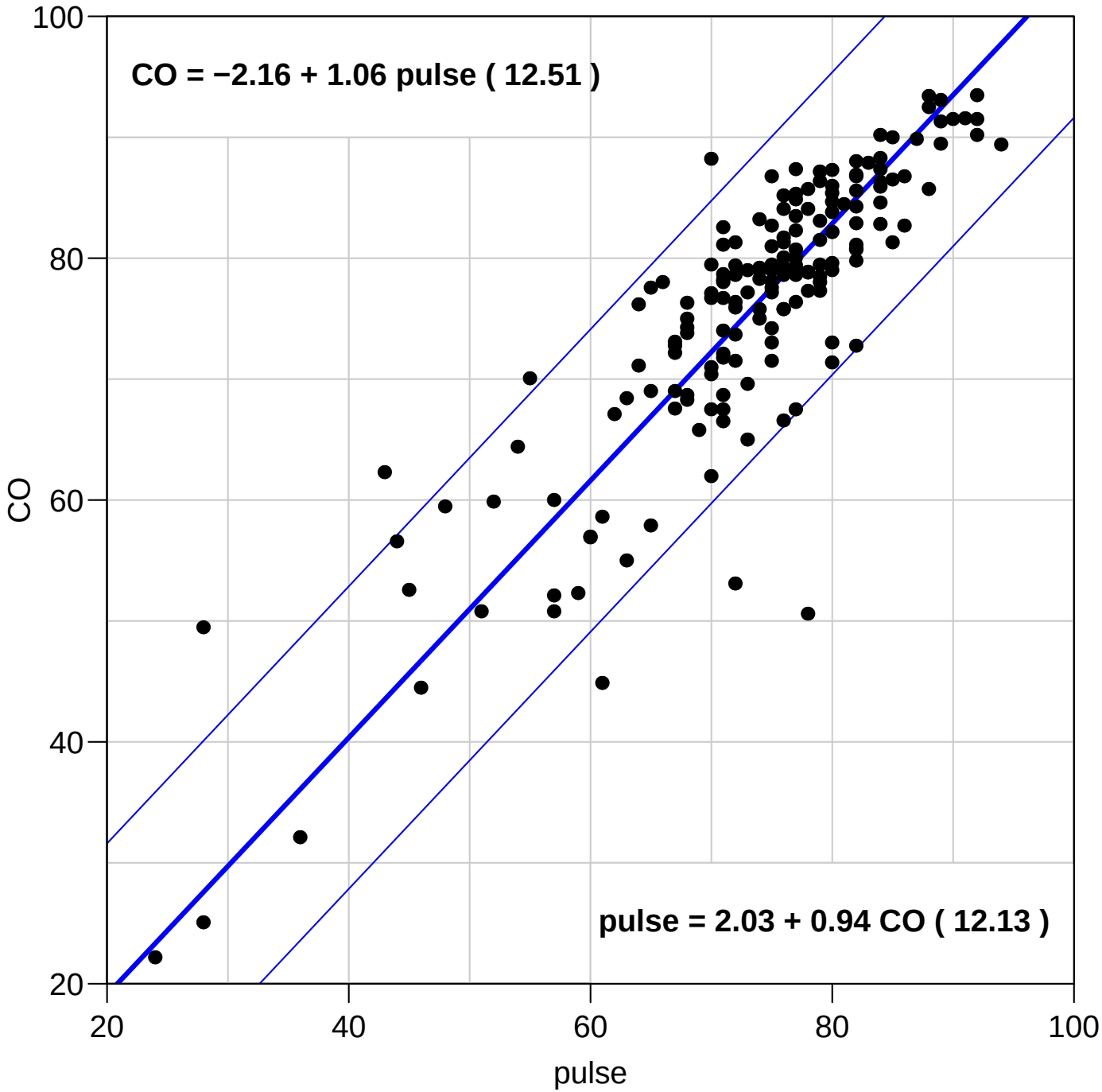
If we do the prediction the other way round $(y_1|y_2)$ we get the same relationship i.e. a line with the inverse slope, β_1/β_2.

The width of the prediction interval in this direction is:

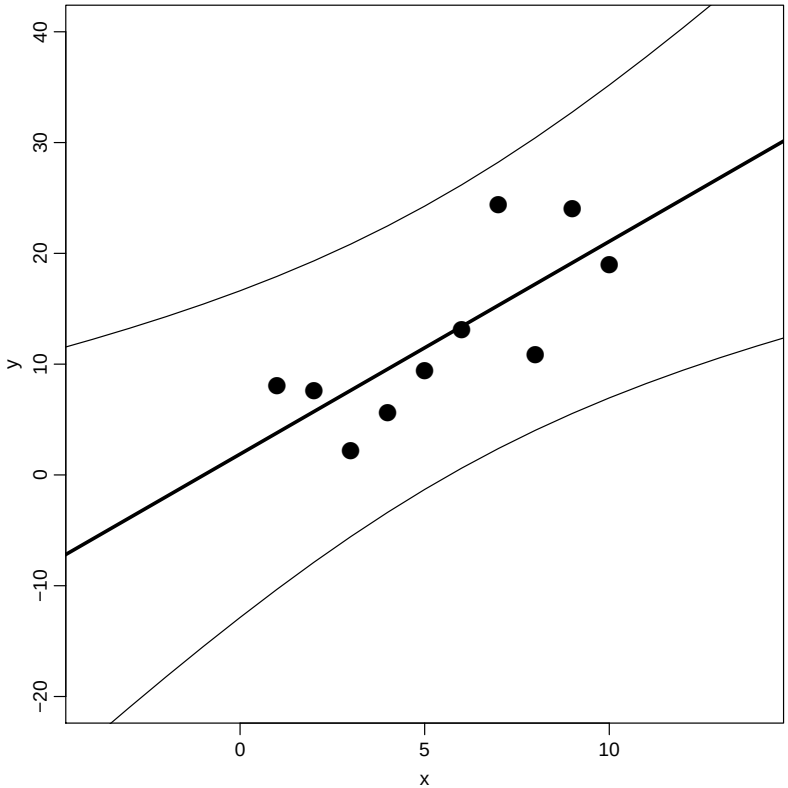
$$2 \times 1.96 \times \sqrt{(\beta_1^2\tau_1^2 + \sigma_1^2) + \left(\frac{\beta_1}{\beta_2}\right)^2(\beta_2^2\tau_2^2 + \sigma_2^2)}$$

$$= 2 \times 1.96 \times \frac{\beta_1}{\beta_2}\sqrt{\left(\frac{\beta_2}{\beta_1}\right)^2(\beta_1^2\tau_1^2 + \sigma_1^2) + (\beta_2^2\tau_2^2 + \sigma_2^2)}$$

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


CO = −2.16 + 1.06 pulse (12.51)
pulse = 2.03 + 0.94 CO (12.13)
CO
pulse
100
80
60
40
20
20
40
60
80
100

What happened to the curvature?



Usually the prediction limits are curved:

$$\hat{y}|x \pm 1.96 \times \hat{\sigma}\sqrt{1 + x'x}$$

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 $\beta_{2.1}$.

Variance components

Thursday 19 February

Bendix Carstensen

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18 February 2009
University of Adelaide

(Var-comp)

Variance components

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

3 variance components / random effects:

- a_{ir}: between replicates within item, ω^2
  $\beta_m\omega$ is the relevant quantity.
- c_{mi}: matrix effect τ_m^2
  $\beta_m\tau_m$ is the relevant quantity.
- e_{mir}: measurement error, residual variation σ_m^2
  σ_m is the relevant quantity.

Variance components

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

The total variance of a measurement is:

$$\sqrt{\beta_m^2\omega^2 + \beta_m^2\tau_m^2 + \sigma_m^2}$$

These are the variance components returned by `AltReg` or `MCmcmcm` using `print.MCmcmc` and shown by `post.MCmcmc`.

Repeatability and reproducibility

Repeatability is based on the difference between measurements made under comparable, though not exactly identical conditions.

Reproducibility is based on the difference between measurements made under comparable, though not exactly identical conditions.

This is a different setting from the one underlying the modelling of data from a comparison experiment.

The exchangeability has no meaning, we are discussing future measurements in different circumstances.

Repeatability and reproducibility

Repeatability: $2.8\sigma_m$:
same individual, same replicate, but not considering the variation that constitute differences between replicates *in the experiment*.

Hence *reproducibility* is not estimable from a classical experiment, unless an extra layer of replication is introduced — i.e. different laboratories.

Alternating regressions

Thursday 19 February

Bendix Carstensen

Analysis of Method Comparison Studies
18 February 2009
University of Adelaide

(Alt-reg)

Alternating random effects regression

Carstensen [5] 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.

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) responses y can be rescaled:

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

Estimation algorithm I

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 paramaters.

The residual variances

The variance components are estimated in the model for the scaled response, and the parameters in that is nok taken into accoundt in the calculation of the residual variance.

Hence the residual variances should be corrected.

All this is implemented in the function `AltReg`

```
> 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
  CO              0.000 -2.159      1.000 1.063   3.521   2.978   2
  pulse           2.031  0.000      0.941 1.000   3.313   2.802   4
```

Transformation of data

Thursday 19 February

Bendix Carstensen

Analysis of Method Comparison Studies
18 February 2009
University of Adelaide

(`Transform`)

If variances are not constant

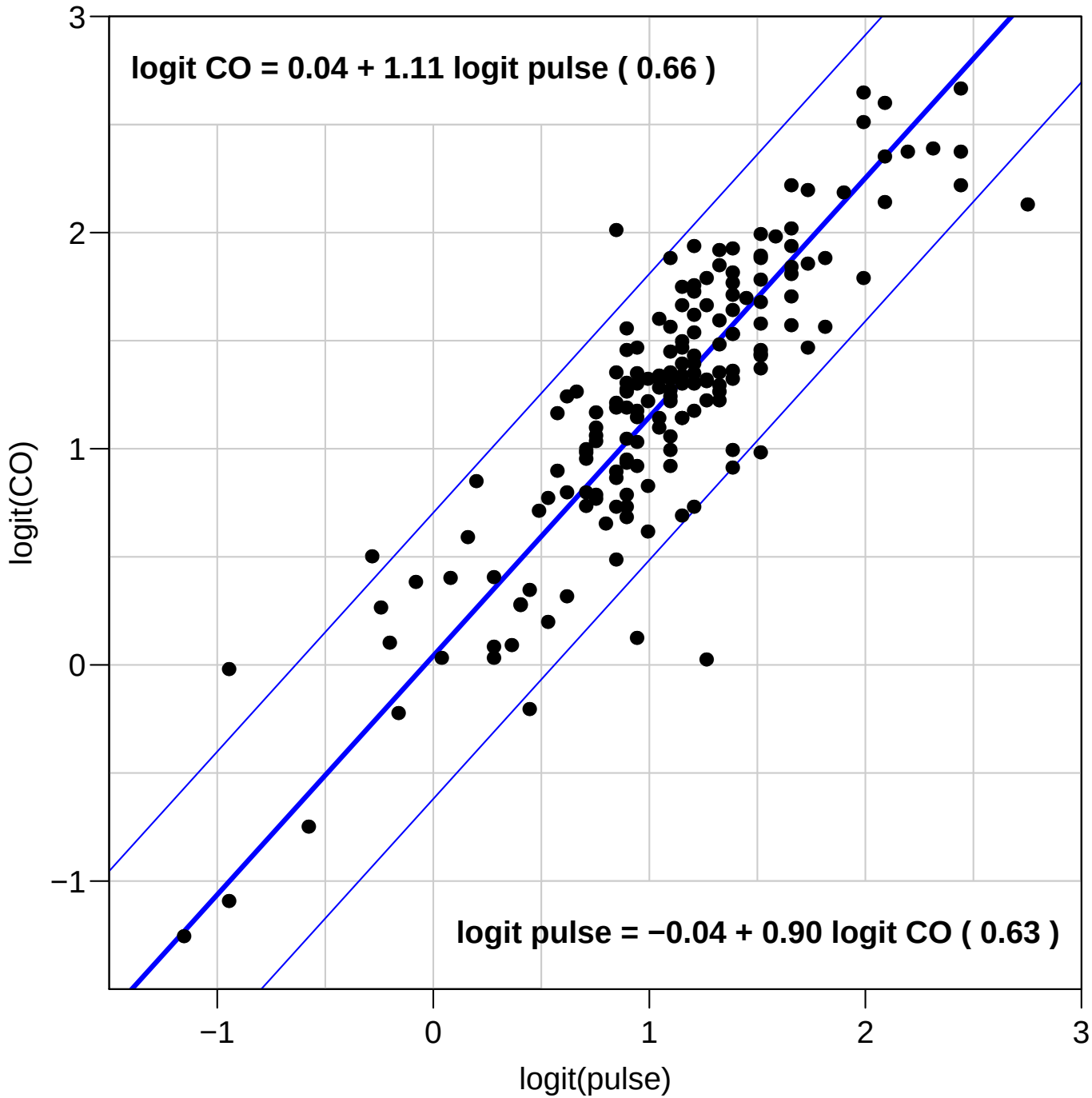
A transformation might help:

```
> 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
```

Analysis on the transformed scale

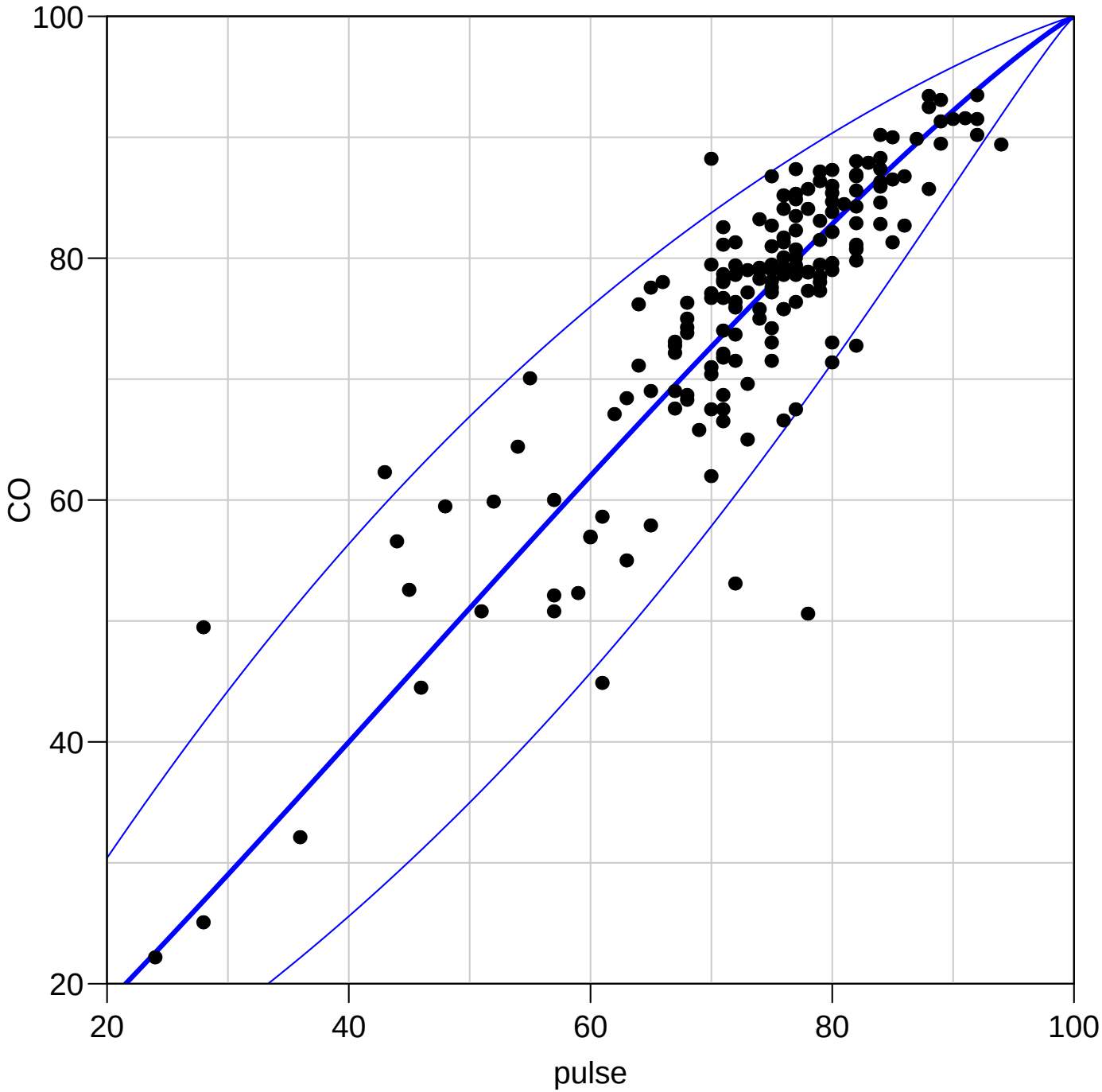
```
> ARoxt <- AltReg(oxt,linked=T,trace=T)
AltReg uses 354 obs. out of 354 in the supplied data.


iteration 1 criterion: 1
       alpha  beta sigma Intercept: CO pulse Slope: CO pulse IxR
CO     0.003 0.998 0.098          1.151 1.151     1.000 0.994   0
pulse -0.003 1.003 0.098          1.151 1.151     1.006 1.000   0

...etc

> round(ARoxt,3)
    From
To   Intercept: CO pulse Slope: CO pulse IxR sd. MxI sd. res.sd.
  CO          0.000 0.042     1.000 1.105   0.232   0.160   0.143
  pulse      -0.038 0.000     0.905 1.000   0.210   0.145   0.191
```

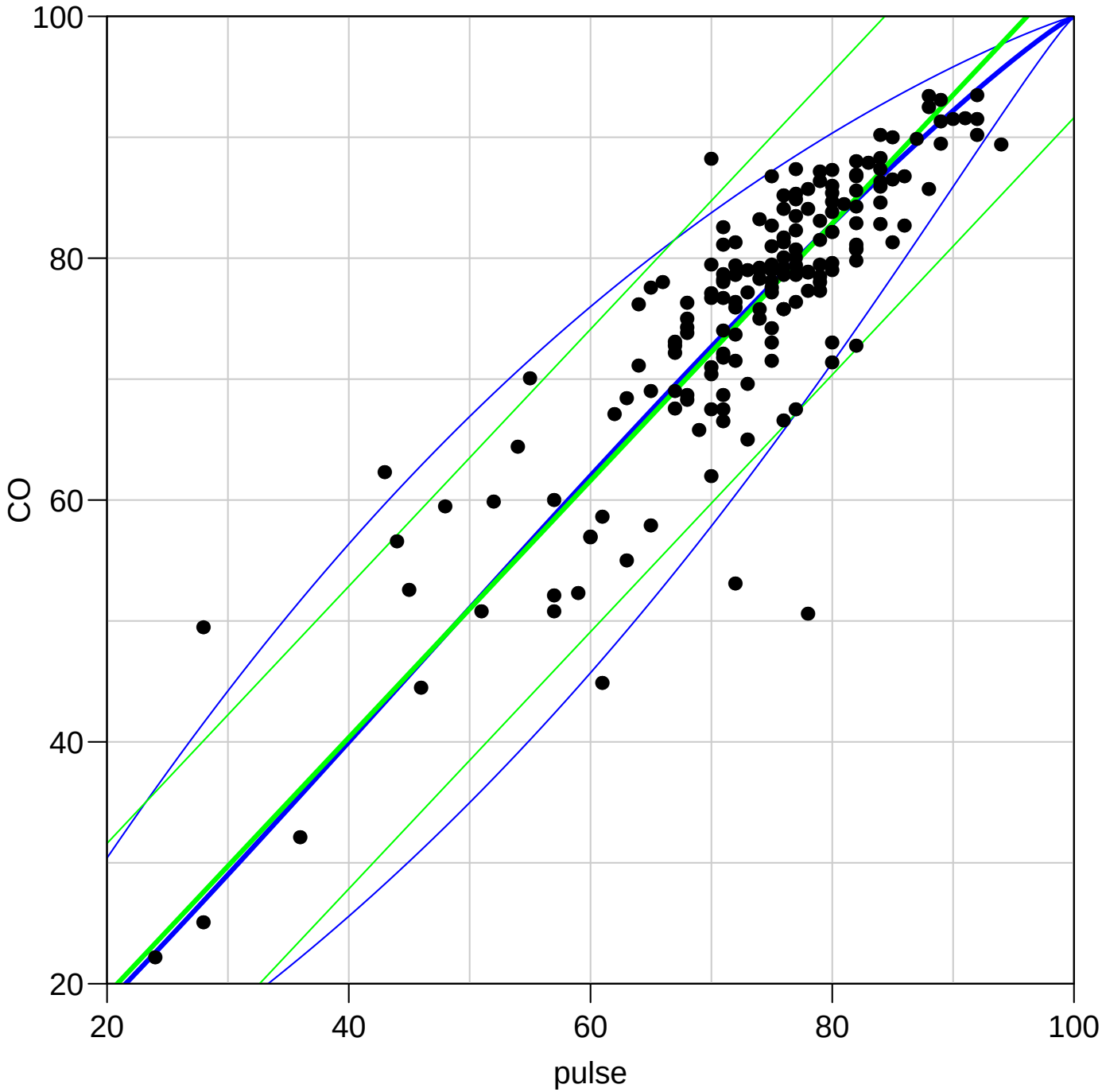
This is an analysis for the transformed data.


logit CO = 0.04 + 1.11 logit pulse (0.66)
logit pulse = −0.04 + 0.90 logit CO (0.63)
logit(CO)
logit(pulse)
3
2
1
0
−1
−1
0
1
2
3

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
```

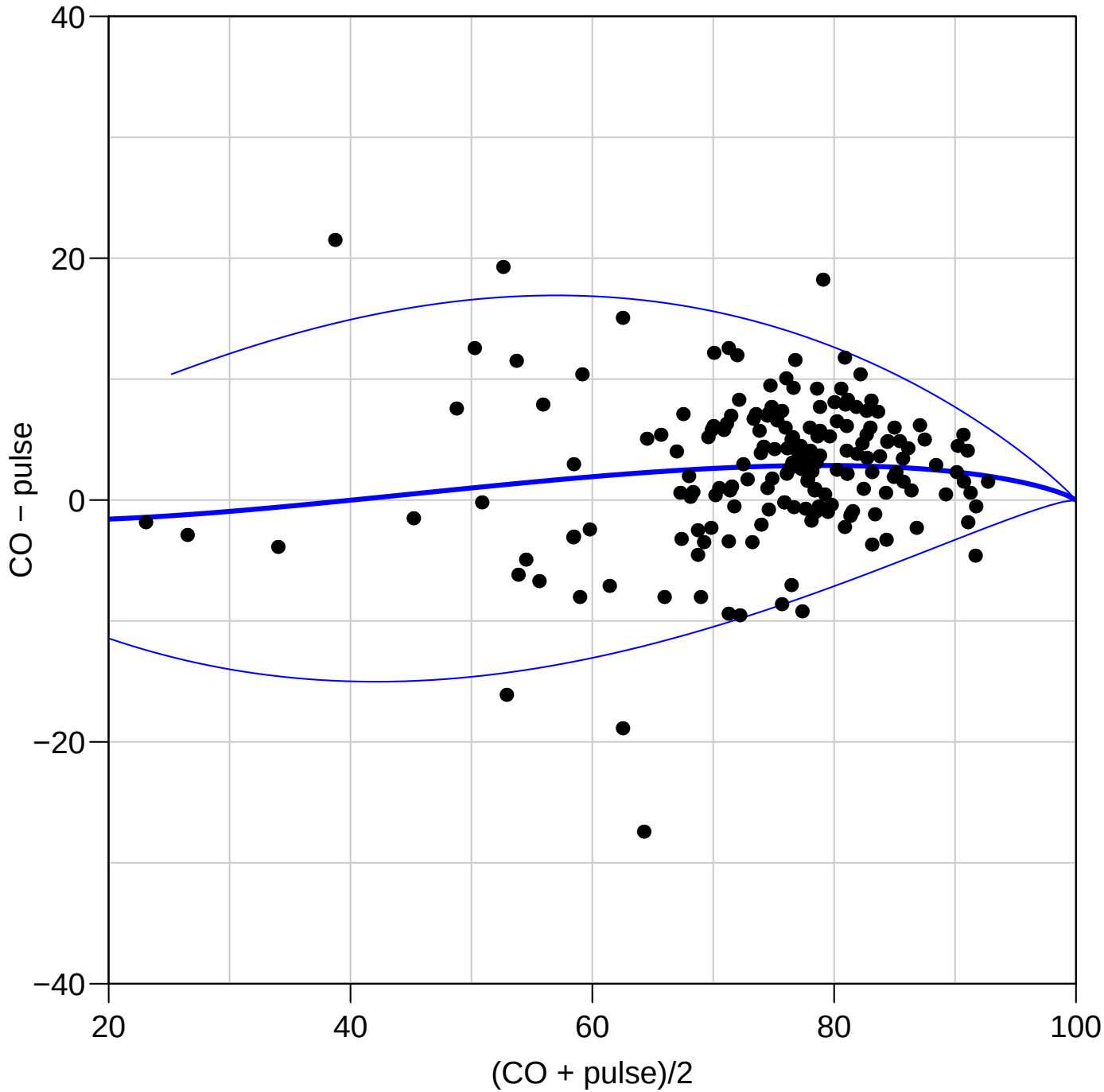

100
80
60
40
20
CO
20
40
60
80
100
pulse


100
80
60
40
20
CO
20
40
60
80
100
pulse

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 )
```


40
20
0
−20
−40
CO − pulse
20
40
60
80
100
(CO + pulse)/2

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.

Statistical methods for assessing agreement between two methods of clinical measurement.

Lancet, i:307–310, 1986.

B Carstensen.

Limits of agreement: How to use the regression of differences on averages.

Technical Report 08.6, Department of Biostatistics, University of Copenhagen, `http://www.pubhealth.ku.dk/bs/publikationer/Research_report_08-6.pdf`, 2008.

B Carstensen, J Simpson, and LC Gurrin.

Statistical models for assessing agreement in method comparison studies with replicate measurements.

International Journal of Biostatistics, 4(1):Article 16, 2008.

Bendix Carstensen.

Comparing and predicting between several methods of measurement.

Biostatistics, 5(3):399–413, Jul 2004.