Comparing Clinical Measurements

or: Statistical Analysis of Method Comparison studies

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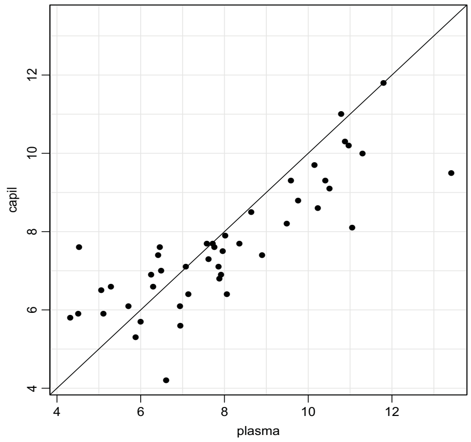
ROeS 2013, Dornbirn, Austria
Monday 9th September
`http://BendixCarstensen.com/MethComp/Dornbirn.2013`

What this is about

- Two (laboratory) methods for measuring the same clinical quantity.
- Persons are measured with both methods.
- Scaled measurements (continuous).
- Errors in both variables.

Glucose measurements



Course outlook

- **Model** based approach
- Explicit **parametric** models:
  - Assumptions are made clear
  - — relaxing assumptions is clear
- **Comparison** of methods:
  — can one replace the other?
- **Conversion** between methods:
  — if measurement is y_1 with method 1, what would it be with method 2?
- Examples from `MethComp` package for **R**.
- Code are in slides

Day schedule 9–12:30

- One measurement by each method
- Linear bias
- Linear s.d.
- Break
- Replicate measurements, exchangeable / linked
- Break (10:30–11:00)
- Replicate measurements and linear bias
- Break
- MCMC methods for estimation of variance components
- Transformation of measurement scale

Comparing two methods with one measurement on each

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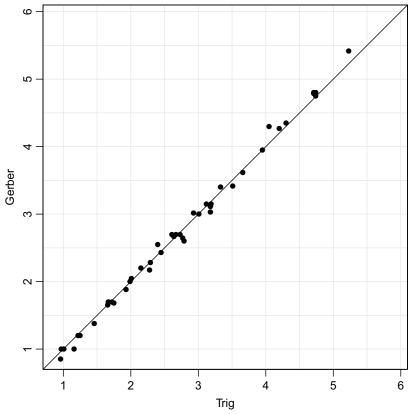
(`Comp-simple`)

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:

$$y_1 = a + by_2$$

```
> library(MethComp)
> data( milk )
> milk <- Meth( milk )

The following variables from the dataframe
"milk" are used as the Meth variables:
meth: meth
item: item
   y: y
         #Replicates
Method            1 #Items #Obs: 90 Values:  min  med  max
  Gerber         45     45       45         0.85 2.67 6.20
  Trig           45     45       45         0.96 2.67 6.21

> par( mar=c(3,3,1,1),mgp=c(3,1,0)/1.6 )
> BA.plot( milk, pl.type="comp", col.line="transparent",
+          lwd=c(3,0,0), axlim=c(1,6)-0.1 )
> abline(0,1)
```

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?

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

- 95% prediction interval for the difference between a measurement by method 1 and one by method 2. [1, 2]
- **Limits of agreement**:

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

Limits of agreement: Interpretation

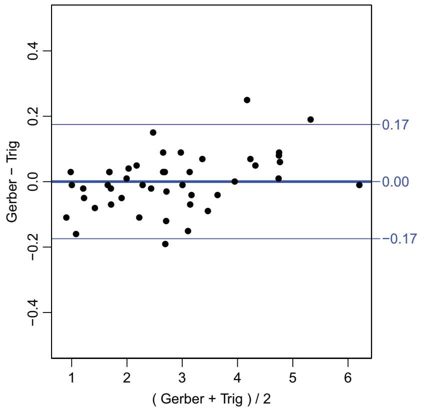
- If a new patient is measured **once** with each of the two methods, the difference between the two values will with 95% probability be within the limits of agreement.
- This is a **prediction** interval for a single (future) difference.
- Interpretation requires a **clinical** input: Are the limits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

Limits of agreement: Test? No!

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:**
     — not interested in the mean difference.
  2. **Clinical input is required.**

Limits of agreement:



Plot differences (D_i) versus averages (A_i).

```
> par( mar=c(3,3,1,3), mgp=c(3,1,0)/1.6 )
> BA.plot( milk, diflim=c(-0.5,0.5), grid=FALSE )
```

Model in “Limits of agreement”

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

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

- 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:

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

- Convert to prediction interval for y_2 given y_1:

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

- Formally, we should replace:

$$2 \quad \rightarrow \quad \text{t}_{0.975}(I-1)\sqrt{1 + 1/I}$$

which equals 2 for $I = 85$

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:

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

In correlation terms:

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

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:

$$y_{mi} = \alpha_m + \mu_i + e_{mi}$$
$$\mathrm{var}(y_m) = \mathrm{var}(\mu_i) + \sigma_m^2$$

and hence the correlation expression is:

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

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)`

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 ($(y_2 - y_1)$ vs. $(y_1 + y_2)/2$)
- 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.

Functions in the `MethComp` package

5 broad categories of functions in `MethComp`:

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

Data manipulation functions

- `Meth` Sets up a `Meth` object — a dataframe in the “long” format, with predefined variable names.
- `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.

Graphical functions (basic)

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

Analysis functions (simple)

- `DA.reg`, regresses the differences on the averages. Also regresses the absolute residuals on the averages to check whether the variance is constant. Returns a `MethComp` object.
- `BA.est` Estimates in the variance components models underlying the concept of limits of agreement, and returns the bias and the variance components. Assumes constant bias between methods. Returns a `MethComp` object.
- `VC.est` The workhorse behind `BA.est`.
- `Deming` Performs Deming regression, i.e. regression with errors in both variables.

Analysis functions (general)

- `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 an `MCmcmc` object.
- `AltReg` Estimates via ad-hoc procedure (alternating regressions) in a model with linear bias between methods. Returns a matrix of estimates with the conversion parameters as well as the variance components. Returns a `MethComp` object.

Reporting functions

- `summary.Meth` Tabulates replicates by methods and items.
- `print.MethComp` Prints a table of conversion equations based on an estimated model data.
- `print.MCmcmc` Prints a table of conversion equation between methods analyzed, with prediction standard deviations.
- `plot.MCmcmc` Plots the conversion lines between methods with prediction limits.
- `post.MCmcmc` Plots smoothed posterior densities for the estimates.
- `trace.MCmcmc` Plots the simulation traces from an `MCmcmc` object.

Non-constant difference

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(Non-const)

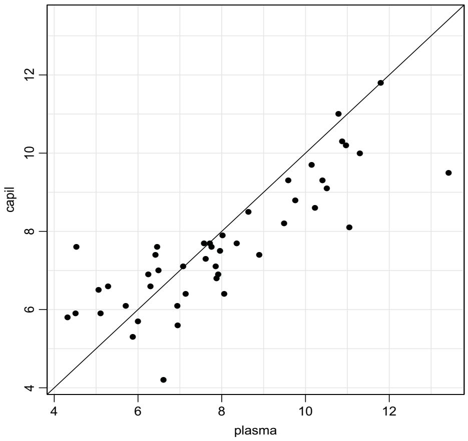
Limits of agreement — assumptions

- 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.

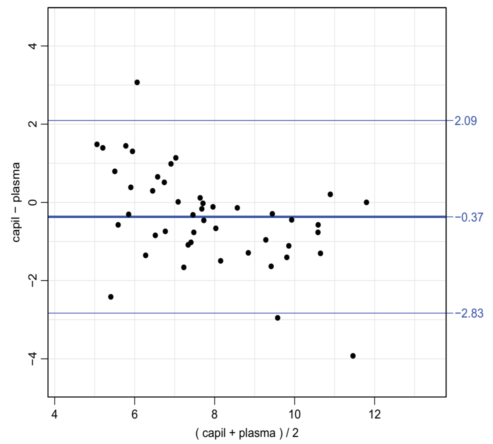
Glucose measurements



```
> options( width=61 )
> library(MethComp)
> data( glucose )
> gluc <-subset( glucose, type %in% levels(type)[c(2,4)] &
+                         meth %in% c("h.cap","o.cap","n.plas1"),
+                         select=c(2,3,4,6) )
> str( gluc )

'data.frame': 472 obs. of  4 variables:
 $ type: Factor w/ 4 levels "blood","plasma",..: 2 4 2 4 2 4 2 4 2 4 ...
 $ item: num  1 1 1 1 1 1 1 1 2 2 ...
 $ time: num  0 0 30 30 60 60 120 120 0 0 ...
 $ y   : num  6.36 5.1 10.3 9.8 13.33 ...

> glu120 <- Meth( subset( gluc, time==120 ), meth="type" )

The following variables from the dataframe
"subset(gluc, time == 120)" are used as the Meth variables:
meth: type
item: item
   y: y
         #Replicates
Method             1 #Items #Obs: 119 Values:  min  med   max
  plasma          73     73         73         4.32 7.92 13.42
  capil           46     46         46         4.20 7.45 11.80
```

```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> BA.plot( glu120, wh.comp=2:1, pl.type="comp",
+          col.line="transparent" )
> abline( 0, 1 )
```

Glucose measurements



```
> par( mar=c(3,3,1,3), mgp=c(3,1,0)/1.6 )
> BA.plot( glu120, wh.comp=2:1, pl.type="BA" )
```

Regress difference on average

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

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:

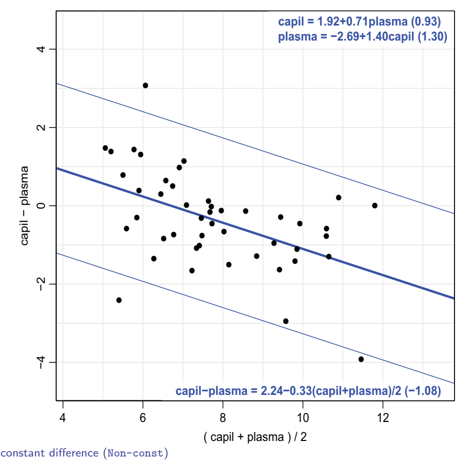
$$y_{2|1} = y_1 + a + bA_i \approx y_1 + a + by_1 = a + (1+b)y_1$$

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



```
> par( mar=c(3,3,1,3), mgp=c(3,1,0)/1.6 )
> BA.plot( glu120, dif.type="lin",wh.comp=2:1, pl.type="BA" )

> par( mar=c(3,3,1,3), mgp=c(3,1,0)/1.6 )
> BA.plot( glu120, dif.type="lin",wh.comp=2:1, pl.type="BA",
+          eqn=TRUE )

Relationships between methods:
 capil-plasma = 2.24-0.33(capil+plasma)/2 (-1.08)
 capil = 1.92+0.71plasma (0.93)
 plasma = -2.69+1.40capil (1.30)
```

Improving the regression of D on A

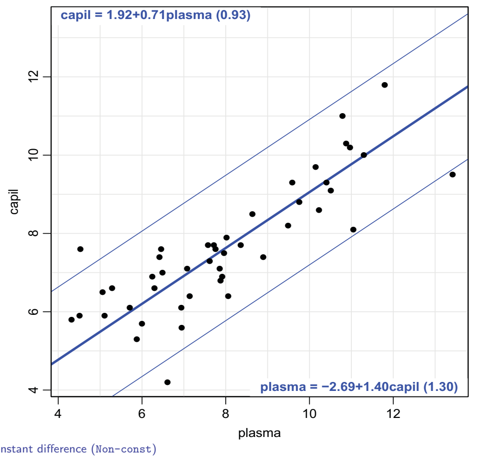
$$y_{2i} - y_{1i} = a + b(y_{1i} + y_{2i})/2 + e_i$$
$$y_{2i}(1 - b/2) = a + (1 + b/2)y_{1i} + e_i$$

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

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

Details found in [5]
This is what comes out of the functions `DA.reg` and `BA.plot`.

Conversion equation with prediction limits



```
> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> BA.plot( glu120, dif.type="lin",wh.comp=2:1, pl.type="conv",
+          eqn=TRUE )

Relationships between methods:
 capil-plasma = 2.24-0.33(capil+plasma)/2 (-1.08)
 capil = 1.92+0.71plasma (0.93)
 plasma = -2.69+1.40capil (1.30)
```

Why does this work?

The general model for the data is:

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

- 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.

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 formally no meaning 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 violations are not that big.
- Implemented in `BA.plot` and in `DA.reg`, which also checks the residuals.

For further details, see [5].

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.

Regressing residuals on average

- Residuals $\sim \mathcal{N}(0,\sigma^2)$
  $\Rightarrow$ absolute residuals half-normal.
- Mean of standard half normal is:

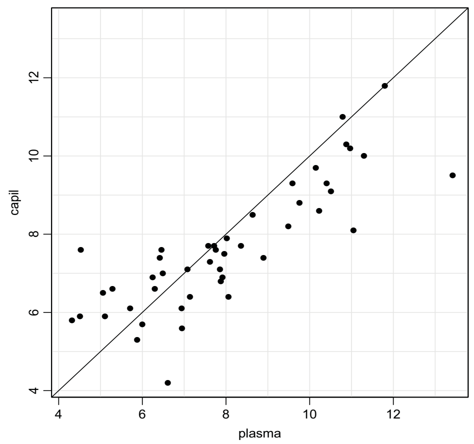
$$\int_0^\infty x(2/\sqrt{2\pi})\exp(-x^2/2)\,\mathrm{d}x = \sqrt{2/\pi}$$

- Mean of absolute residuals is $\sigma\sqrt{2/\pi}$
- Linear relationship of absolute residuals (R_i) to averages (A_i):

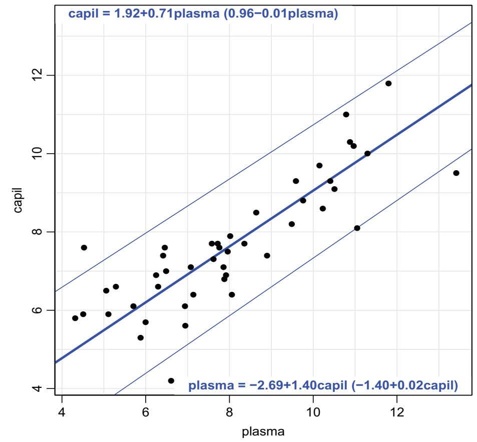
$$R_i = a + bA_i \quad\Leftrightarrow\quad \sigma(A) \approx a\sqrt{\pi/2} + b\sqrt{\pi/2}A$$

- Implemented in `DA.reg`.

Glucose measurements



Variable standard deviation



```
> (zz <- DA.reg( glu120 ) )

 Conversion between methods:
                alpha   beta sd.pred beta=1 int(t-f) slope(t-f) sd(t-f) int(sd)
To:    From:
plasma plasma   0.000  1.000      NA     NA    0.000      0.000      NA      NA
       capil   -2.695  1.402   1.302  0.000   -2.244      0.335   1.084   1.138
capil  plasma   1.922  0.713   0.928  0.000    2.244     -0.335  -1.084   1.138
       capil    0.000  1.000      NA     NA    0.000      0.000      NA      NA

> round( ftable(zz$Conv[,,-(1:5)]), 3 )

               slope(t-f) sd(t-f) int(sd) slope(sd)   sd=K LoA-lo LoA-up
To:    From:
plasma plasma       0.000      NA      NA        NA     NA     NA     NA
       capil        0.335   1.084   1.138    -0.015  0.833 -2.095  2.833
capil  plasma      -0.335  -1.084   1.138    -0.015  0.833 -2.833  2.095
       capil        0.000      NA      NA        NA     NA     NA     NA

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> BA.plot( glu120, wh.comp=2:1, pl.type="BA", dif.type="const",
+          sd.type="lin", eqn=TRUE )
```

```
Relationships between methods:
 capil-plasma = -0.37 (1.70-0.07Avg.)
 capil = -0.37+plasma (1.65-0.07plasma)
 plasma = 0.37+capil (-1.75+0.07capil)

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> BA.plot( glu120, wh.comp=2:1, pl.type="BA",
+          dif.type="lin", sd.type="lin", eqn=TRUE )

Relationships between methods:
 capil-plasma = 2.24-0.33(capil+plasma)/2 (1.14-0.02Avg.)
 capil = 1.92+0.71plasma (0.96-0.01plasma)
 plasma = -2.69+1.40capil (-1.40+0.02capil)

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> BA.plot( glu120, wh.comp=2:1, pl.type="comp",
+          dif.type="lin", sd.type="lin", eqn=TRUE )

Relationships between methods:
 capil-plasma = 2.24-0.33(capil+plasma)/2 (1.14-0.02Avg.)
 capil = 1.92+0.71plasma (0.96-0.01plasma)
 plasma = -2.69+1.40capil (-1.40+0.02capil)
```

Variable mean and standard deviation

- 2-step procedure:
  - Regress D_i on A_i.
  - Regress R_i (absolute residuals) on A_i
- Can be done using quadratic rather than linear terms, or even splines.
- Allows very flexible form of the relationships between differences and averages
- —and flexible form of the s.d. to the mean.
- The relationship $D\tilde{A}$ is easily back-transformed to a relationship $y_1\tilde{y}_2$, with prediction intervals.
- Beware: **over-modelling!**

Comparing two methods with replicate measurements

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(comp-repl)

Replicate measurements on each item

Fat data; **exchangeable** replicates:

```
item repl  KL  SL
   1    1 4.5 5.0
   1    2 4.7 4.9
   1    3 4.4 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
```

Replicate measurements on each item

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 77.2    73
   1    2 78.0    71
   1    3 76.4    72
   2    1 68.7    68
   2    2 67.6    67
   2    3 68.3    68
```

Extension of the model: exchangeable replicates

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir}$$
$$\mathrm{s.d.}(c_{mi}) = \tau_m \quad \text{— “matrix”-effect}$$
$$\mathrm{s.d.}(e_{mir}) = \sigma_m \quad \text{— measurement error}$$

- 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: linked replicates

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

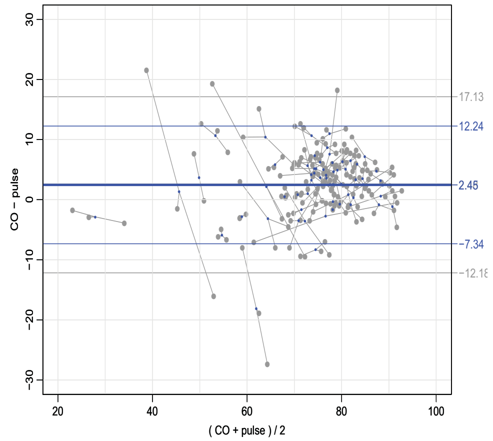
- Still assumes difference between methods constant.
- Replicates **linked** between methods: a_{ir} is common across methods; first replicate on a person is made under similar conditions for all methods, second too etc.

Replicate measurements

Three approaches to LoA with replicate measurements:

1. Means over replicates within each method by item stratum.
2. Replicates within item are taken as items.
3. Fit the model and use it for the LoA:
   - The model is a standard linear mixed model with separate variances per method.
   - The model is fitted using `BA.est(data,linked=TRUE)` — later.

Oximetry data



```
> library(MethComp)
> data( ox )
> ox <- Meth( ox, print=FALSE )
> 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

> par( mar=c(3,3,1,3), mgp=c(3,1,0)/1.6 )
> BA.plot( ox, pl.type="BA",
+       axlim=c(20,100), diflim=c(-30,30) )

> par( mar=c(3,3,1,3), mgp=c(3,1,0)/1.6 )
> BA.plot( ox, pl.type="BA", col.points=gray(0.5), repl.conn=TRUE,
+       axlim=c(20,100), diflim=c(-30,30), col.lines=gray(0.5) )

> par( mar=c(3,3,1,3), mgp=c(3,1,0)/1.6 )
> BA.plot( ox, pl.type="BA", col.points=gray(0.6), repl.conn=TRUE,
+       axlim=c(20,100), diflim=c(-30,30), col.lines=gray(0.6) )
> par( new=TRUE )
> BA.plot( mean(ox), pl.type="BA", col.points="blue", cex=0.5,
+          axlim=c(20,100), diflim=c(-30,30) )
```

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:

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

- In the model the correct limits of agreement would be:

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

Wrong or almost right

- $\text{var}(y_{1jr} - y_{2jr}) = \tau_1^2 + \tau_2^2 + \sigma_1^2 + \sigma_2^2$ — note that the term $a_{ir} - a_{ir}$ cancels because we are referring to the *same* replicate.
- If we are using means of replicates to form the differences we have:

$$
\begin{aligned}
\bar{d}_i = \bar{y}_{1i\cdot} - \bar{y}_{2i\cdot} &= \alpha_1 - \alpha_2 + \frac{\sum_r a_{ir}}{R_{1i}} - \frac{\sum_r a_{ir}}{R_{2i}} \\
&\quad + c_{1i} - c_{2i} + \frac{\sum_r e_{1ir}}{R_{1i}} - \frac{\sum_r e_{2ir}}{R_{2i}} \\
\Rightarrow \quad \text{var}(\bar{d}_i) &= \tau_1^2 + \tau_2^2 + \sigma_1^2/R_{1i} + \sigma_2^2/R_{2i} \\
&< \tau_1^2 + \tau_2^2 + \sigma_1^2 + \sigma_2^2
\end{aligned}
$$

(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.
- 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?

- Exchangeable replicates: not clear how to produce the differences with 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.

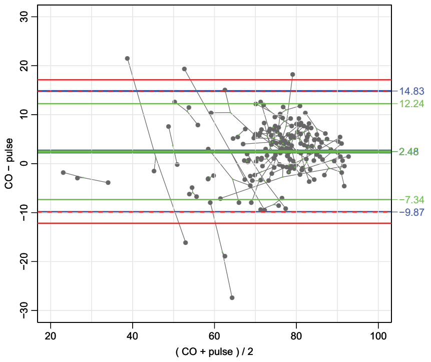
Further details, see [6].

Oximetry data

Linked replicates used as items

Mean over replicates as items

Limits based on model — dashed line assuming linked, full exchangeable replicates



```
> ( ox.link <- BA.est( ox, linked=TRUE ) )

 Conversion between methods:
              alpha    beta sd.pred  LoA-lo  LoA-up
To:   From:
CO    CO      0.000   1.000   3.146  -6.293   6.293
      pulse   2.470   1.000   6.169  -9.867  14.808
pulse CO     -2.470   1.000   6.169 -14.808   9.867
      pulse   0.000   1.000   5.649 -11.298  11.298

 Variance components (sd):
        IxR   MxI   res
CO    3.416 2.928 2.225
pulse 3.416 2.928 3.994

> ( ox.exch <- BA.est( ox, linked=FALSE ) )
```

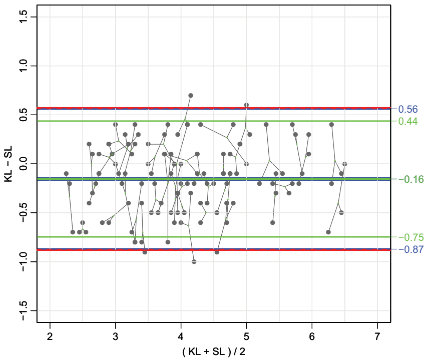
```
 Conversion between methods:
              alpha    beta sd.pred  LoA-lo  LoA-up
To:   From:
CO    CO      0.000   1.000   5.755 -11.509  11.509
      pulse   2.476   1.000   7.326 -12.175  17.127
pulse CO     -2.476   1.000   7.326 -17.127  12.175
      pulse   0.000   1.000   7.417 -14.835  14.835

 Variance components (sd):
      IxR   MxI   res
CO      0 2.191 4.069
pulse   0 2.191 5.245

> par( mar=c(3,3,1,3), mgp=c(3,1,0)/1.6 )
> BA.plot( ox, pl.type="BA", model=NULL,
+          col.points=gray(0.4), repl.conn=TRUE,
+          axlim=c(20,100), diflim=c(-30,30), col.lines="blue",
+          lwd=c(6,3,3) )
> par( new=TRUE )
> BA.plot( mean(ox), pl.type="BA", col.points="green",
+          cex.points=0.3, axlim=c(20,100), diflim=c(-30,30),
+          col.lines="green", lwd=c(4,2,2))
> abline( h=-ox.link[["LoA"]][2:3], col="red", lwd=2, lty=2 )
> abline( h=-ox.exch[["LoA"]][2:3], col="red", lwd=2, lty=1 )
```

Visceral fat data (exchangeable replicates)

Randomly paired replicates used as items

Mean over replicates as items

Limits based on model — dashed line assuming linked, full exchangeable replicates



```
> data( fat )
> vis <- Meth( fat, 2, 1, 3, 5 )

The following variables from the dataframe
"fat" are used as the Meth variables:
meth: Obs
item: Id
repl: Rep
   y: Vic
       #Replicates
Method        3 #Items #Obs: 258 Values:  min med max
    KL       43     43       129           2.0 3.9 6.5
    SL       43     43       129           2.3 4.1 6.7

> ( vis.link <- BA.est( vis, linked=TRUE ) )

 Conversion between methods:
            alpha   beta sd.pred LoA-lo LoA-up
To: From:
KL  KL      0.000  1.000   0.264 -0.528  0.528
    SL     -0.155  1.000   0.360 -0.874  0.564
SL  KL      0.155  1.000   0.360 -0.564  0.874
    SL      0.000  1.000   0.235 -0.471  0.471

 Variance components (sd):
    IxR   MxI   res
KL 0.048 0.183 0.187
SL 0.048 0.183 0.166
```

```
> ( vis.exch <- BA.est( vis, linked=FALSE ) )

 Conversion between methods:
            alpha   beta sd.pred LoA-lo LoA-up
To: From:
KL  KL      0.000  1.000   0.273 -0.545  0.545
    SL     -0.155  1.000   0.364 -0.883  0.573
SL  KL      0.155  1.000   0.364 -0.573  0.883
    SL      0.000  1.000   0.245 -0.490  0.490

 Variance components (sd):
   IxR   MxI   res
KL   0 0.181 0.193
SL   0 0.181 0.173

> par( mar=c(3,3,1,3), mgp=c(3,1,0)/1.6 )
> BA.plot( vis, pl.type="BA", model=NULL,
+          col.points=gray(0.4), repl.conn=TRUE,
+          axlim=c(2,7), diflim=c(-3,3)/2, col.lines="blue",
+          lwd=c(6,3,3) )
> par( new=TRUE )
> BA.plot( mean(vis), pl.type="BA", col.points="green",
+          cex.points=0.3, axlim=c(2,7), diflim=c(-3,3)/2,
+          col.lines="green", lwd=c(4,2,2))
> abline( h=-vis.link[["LoA"]][2:3], col="red", lwd=2, lty=2 )
> abline( h=-vis.exch[["LoA"]][2:3], col="red", lwd=2, lty=1 )
```

Repeatability and reproducibility

Bendix Carstensen

MethComp
Monday 9th September
ROeS 2013, Dornbirn, Austria
`http://BendixCarstensen.com/MethComp/Dornbirn.2013`

(Repro)

Accuracy of a measurement method

(ISO 5625)

- 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 measurements.
- Suppose the variance of the measurement is σ^2:

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

— standard error of difference: $\sqrt{2}\sigma$,
confidence interval for the difference:

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

- This is called the reproducibility coefficient or simply the **reproducibility**.
  (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.

Coefficient of variation

- Defined as s.d. relative to mean: $\text{CV} = \sigma/\mu$
- Measurements with varying mean and s.d. may still have constant CV.
- Assumption of proportionality between mean and s.d. across the range of x:
  $\text{s.d.}(x) = \text{CV}\sigma(x)$
  — implies that measurements are positive.
- LoA could be:

$$\mu \pm 2\text{CV}\mu$$

- But what if $\text{CV} > 0.5$ — lower bound < 0?
- Immaterial — depends on the degree of confidence chosen.

Coefficient of variation

- σ proportional to μ
- ⇒ confidence intervals should be multiplicative: $\mu \overset{\times}{\div} \text{erf}$:
- Specifically:

$$\text{s.d.}\big(\log(Y)\big) \approx \sigma \times \left.\frac{\mathrm{d}\log(y)}{\mathrm{d}y}\right|_{y=\mu} = \sigma/\mu = \text{CV}$$

- Using CV is just using the log-scale:

$$\text{s.d.}(\log(X)) = \sigma\frac{\mathrm{d}\log(x)}{\mathrm{d}x}$$

Coefficient of variation

- If CV is small:
  CV is the same as the s.d. of the log-transformed data.
- If CV is large:
  CV is the **not** same as the s.d. of the log-transformed data.
- But it is the log-transformed analysis that is meaningful.
- Empirical question if this gives a better model.
- It is not a different model — just the same model on a transformed scale.

Linear bias between methods

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`http://BendixCarstensen.com/MethComp/Dornbirn.2013`

`(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.
- Variance of a_{ir} does not depend on m — reporting scaled to each of the methods by the corresponding β_m.
- Implies that $\omega = \text{s.d.}(a_{ir})$ 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.

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

- Matrix-effect: Each item reacts differently to each method.
- If only two methods:
  - 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.

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

- 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.
- a_{ir} nuisance parameters — $(\mu_i + a_{ir})$ is the "true" value underlying measurements y_{mir}.

Extended model

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

- Not a standard linear mixed model.
- Does not fit into usual software.
- Fitted in `BUGS`, via `MCmcmc`.
- …or `AltReg` — later

```
> options( width=61 )
> library(MethComp)
> data( ox )
> ox <- Meth( ox )

The following variables from the dataframe
"ox" are used as the Meth variables:
meth: meth
item: item
repl: repl
   y: y
        #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

> system.time( MCox <- MCmcmc( ox, IxR=TRUE ) )
```

```
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
  pulse   1   4  56     61       177         24.0 75.0 94.0

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.

Initialization and burn-in:
Compiling model graph
   Resolving undeclared variables
   Allocating nodes
   Graph Size: 2868

Initializing model

Sampling:
   user  system elapsed
  14.62    0.13   15.27
```

```
> MCox

 Conversion between methods:
              alpha   beta sd.pred int(t-f) slope(t-f) sd(t-f)
To:   From:
CO    CO      0.000 1.000   2.388    0.000      0.000   2.388
      pulse  -9.536 1.166   5.291   -8.807      0.153   4.886
pulse CO      8.181 0.858   4.538    8.807     -0.153   4.886
      pulse   0.000 1.000   6.046    0.000      0.000   6.046

 Variance components (sd):
       s.d.
Method    IxR   MxI   res
  CO    3.775 3.191 1.689
  pulse 3.240 2.738 4.275

Variance components with 95 % cred.int.:
    method    CO             pulse
    qnt      50%  2.5% 97.5%   50%  2.5% 97.5%
SD
IxR        3.775 3.071 4.495 3.240 2.598 3.917
MxI        3.191 2.309 4.201 2.738 1.948 3.596
res        1.689 0.379 2.758 4.275 3.654 4.981
tot        5.254 4.604 6.044 6.056 5.457 6.753

Mean parameters with 95 % cred.int.:
                   50%    2.5%  97.5% P(>0/1)
alpha[pulse.CO]  8.189  -1.845 15.648   0.953
alpha[CO.pulse] -9.527 -20.381  1.874   0.047
```

```
beta[pulse.CO]   0.858   0.765  0.989   0.016
beta[CO.pulse]   1.166   1.011  1.307   0.984

 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.

> MethComp( MCox )

 Conversion between methods:
              alpha   beta sd.pred int(t-f) slope(t-f) sd(t-f)
To:   From:
CO    CO      0.000 1.000   2.388    0.000      0.000   2.388
      pulse  -9.536 1.166   5.291   -8.807      0.153   4.886
pulse CO      8.181 0.858   4.538    8.807     -0.153   4.886
      pulse   0.000 1.000   6.046    0.000      0.000   6.046

 Variance components (sd):
       s.d.
Method    IxR   MxI   res
  CO    3.775 3.191 1.689
  pulse 3.240 2.738 4.275
```

Converting between methods

Bendix Carstensen

MethComp
Monday 9th September
ROeS 2013, Dornbirn, Austria
`http://BendixCarstensen.com/MethComp/Dornbirn.2013`

`(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:

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

- Intercept: $\alpha_{2|1} = \alpha_2 - \alpha_1 \dfrac{\beta_2}{\beta_1}$
- Slope: $\beta_{2|1} = \dfrac{\beta_2}{\beta_1}$
- Invariant under linear transform of μ:

$$a + b\mu_i \rightarrow \tilde{\mu}_i \quad \Rightarrow \quad \alpha_m + \beta_m\mu_i \rightarrow \tilde{\alpha}_m + \tilde{\beta}_m\tilde{\mu}_i$$

where: $\tilde{\alpha}_m = \alpha_m - a\beta_m/b, \quad \tilde{\beta}_m = \beta_m/b$

- $\Rightarrow$ the conversion is invariant too:

$$
\begin{aligned}
\alpha_{2|1} &= \tilde{\alpha}_2 - \tilde{\alpha}_1 \frac{\tilde{\beta}_2}{\tilde{\beta}_1} \\
\beta_{2|1} &= \frac{\tilde{\beta}_2}{\tilde{\beta}_1}
\end{aligned}
$$

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

The prediction s.d. is:

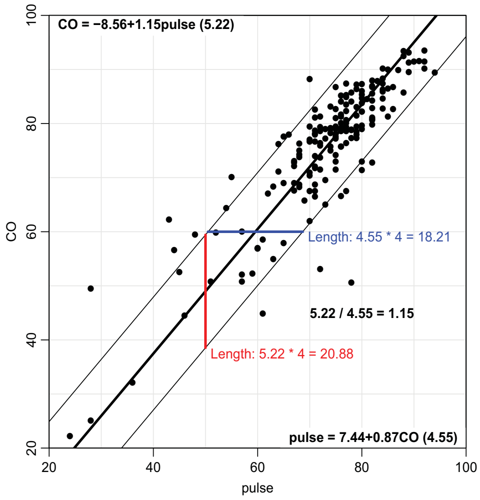
$$\sigma_{2|1} = \sqrt{\left(\frac{\beta_2}{\beta_1}\right)^2(\beta_1^2\tau_1^2 + \sigma_1^2) + (\beta_2^2\tau_2^2 + \sigma_2^2)}$$

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):

$$
\begin{aligned}
\sigma_{1|2} &= \sqrt{(\beta_1^2\tau_1^2 + \sigma_1^2) + \left(\frac{\beta_1}{\beta_2}\right)^2(\beta_2^2\tau_2^2 + \sigma_2^2)} \\
&= \frac{\beta_1}{\beta_2}\sqrt{\left(\frac{\beta_2}{\beta_1}\right)^2(\beta_1^2\tau_1^2 + \sigma_1^2) + (\beta_2^2\tau_2^2 + \sigma_2^2)} = \frac{\beta_1}{\beta_2}\sigma_{2|1}
\end{aligned}
$$

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



```
> options( width=61 )
> library(MethComp)
> data( ox )
> ox <- Meth( ox )

The following variables from the dataframe
"ox" are used as the Meth variables:
meth: meth
item: item
repl: repl
   y: y
        #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

> system.time( MCox <- MCmcmc( ox, IxR=TRUE ) )
```

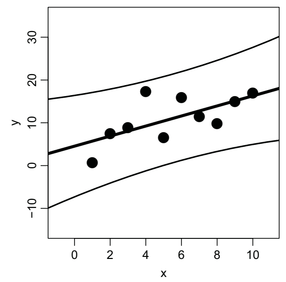
```
Comparison of 2 methods, using 354 measurements
on 61 items, with up to 3 replicate measurements,
(replicate values are in the set: 1 2 3 )
( 2 * 61 * 3 = 366 ):

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
  pulse   1  4  56     61       177         24.0 75.0 94.0

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.

Initialization and burn-in:
Compiling model graph
   Resolving undeclared variables
   Allocating nodes
   Graph Size: 2868

Initializing model

Sampling:
   user  system elapsed
  14.68    0.05   14.78
```

```
> ( Mox <- MethComp( MCox ) )

 Conversion between methods:
              alpha   beta sd.pred int(t-f) slope(t-f) sd(t-f)
To:   From:
CO    CO      0.000  1.000   2.470    0.000      0.000   2.470
      pulse  -8.562  1.151   5.220   -7.962      0.140   4.853
pulse CO      7.439  0.869   4.552    7.962     -0.140   4.872
      pulse   0.000  1.000   6.030    0.000      0.000   6.030

 Variance components (sd):
       s.d.
Method    IxR   MxI   res
  CO    3.744 3.090 1.747
  pulse 3.272 2.716 4.264

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plot( Mox, points=TRUE, axlim=c(20,100), xaxs="i", yaxs="i" )

Relationships between methods:
 CO-pulse = -7.96+0.14(CO+pulse)/2 (4.85)
 CO = -8.56+1.15pulse (5.22)
 pulse = 7.44+0.87CO (4.55)

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plot( Mox, points=TRUE, axlim=c(20,100), xaxs="i", yaxs="i" )
```

```
Relationships between methods:
 CO-pulse = -7.96+0.14(CO+pulse)/2 (4.85)
 CO = -8.56+1.15pulse (5.22)
 pulse = 7.44+0.87CO (4.55)

> segments( 50, Mox$Conv["CO","pulse","alpha"  ] +
+               Mox$Conv["CO","pulse","beta"   ]*50 -
+               Mox$Conv["CO","pulse","sd.pred"]*2,
+           50, Mox$Conv["CO","pulse","alpha"  ] +
+               Mox$Conv["CO","pulse","beta"   ]*50 +
+               Mox$Conv["CO","pulse","sd.pred"]*2,
+           col="red", lwd=3 )
> text( 51, Mox$Conv["CO","pulse","alpha"  ] +
+           Mox$Conv["CO","pulse","beta"   ]*50 -
+           Mox$Conv["CO","pulse","sd.pred"]*2.02,
+       paste( "Length:", formatC(Mox$Conv["CO","pulse","sd.pred"],
+                                 format="f", digits=2),
+              "* 4 =", formatC(Mox$Conv["CO","pulse","sd.pred"]*4,
+                                 format="f", digits=2) ),
+       col="red", adj=c(0,1) )
> segments( Mox$Conv["pulse","CO","alpha"  ] +
+           Mox$Conv["pulse","CO","beta"   ]*60 -
+           Mox$Conv["pulse","CO","sd.pred"]*2, 60,
+           Mox$Conv["pulse","CO","alpha"  ] +
+           Mox$Conv["pulse","CO","beta"   ]*60 +
+           Mox$Conv["pulse","CO","sd.pred"]*2, 60,
+           col="blue", lwd=3 )
> text( Mox$Conv["pulse","CO","alpha"  ] +
+       Mox$Conv["pulse","CO","beta"   ]*60 +
```

```
+       Mox$Conv["pulse","CO","sd.pred"]*2 + 1, 60,
+       paste( "Length:", formatC(Mox$Conv["pulse","CO","sd.pred"],
+                                 format="f", digits=2),
+              "* 4 =", formatC(Mox$Conv["pulse","CO","sd.pred"]*4,
+                                 format="f", digits=2) ),
+       col="blue", adj=c(0,1) )
> text( 70, 45, paste( formatC( Mox$Conv["CO","pulse","sd.pred"],
+                               format="f", digits=2 ), "/",
+                      formatC( Mox$Conv["pulse","CO","sd.pred"],
+                               format="f", digits=2 ), "=",
+                      formatC( Mox$Conv["CO","pulse","beta"],
+                               format="f", digits=2 ) ),
+       adj=0, font=2 )
```

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 $\beta_{2|1}$.

```
> set.seed(17676)
> par(mar=c(3,3,1,1),mgp=c(3,1,0)/1.6)
> x <- 1:10
> y <- 3 + 1.6*x + rnorm(x,,6)
> m0 <- lm(y~x)
> plot(y~x,pch=16,ylim=c(-15,35),xlim=c(-1,11),cex=2)
> nx <- seq(-3,13,,200)
> matlines( nx, predict( m0, interval="pred", newdata=data.frame(x=nx)),
+           lwd=c(4,2,2), col="black", lty=1 )

> set.seed(17676)
> par(mar=c(3,3,1,1),mgp=c(3,1,0)/1.6)
> x <- seq(1,10,,100)
> y <- 3 + 1.6*x + rnorm(x,,6)
> m0 <- lm(y~x)
> plot(y~x,pch=16,ylim=c(-15,35),xlim=c(-1,11),cex=0.7)
> nx <- seq(-3,13,,200)
> matlines( nx, predict( m0, interval="pred", newdata=data.frame(x=nx)),
+           lwd=c(4,2,2), col="black", lty=1 )
```

Comparing to a gold standard

- The prediction s.d. is:

$$\sigma_{2|1} = \sqrt{\left(\frac{\beta_2}{\beta_1}\right)^2 (\beta_1^2\tau_1^2 + \sigma_1^2) + (\beta_2^2\tau_2^2 + \sigma_2^2)}$$

- If method 1 is the gold standard, known without error, *i.e.* **assumed**: $\tau_1 = \sigma_1 = 0$
- Estimate relationship by regressing y_2 on y_1, deriving τ_2 and σ_2 — standar linear regresssion.
- Prediction of y_1 (what would the gold standard give?):
- Limits for $y_2|y_1$, but used the other way.

Alternating regressions

Bendix Carstensen

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Monday 9th September
ROeS 2013, Dornbirn, Austria
http://BendixCarstensen.com/MethComp/Dornbirn.2013

(alt-reg)

Alternating random effects regression

Carstensen [3] 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 that:

- 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 [4]

Alternating random effects regression

The correctly formulated version of the slightly more general model:

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

- 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.

```
> options( width=100 )
> library(MethComp)
> data( ox )
> ox <- Meth( ox )

The following variables from the dataframe
"ox" are used as the Meth variables:
meth: meth
item: item
repl: repl
   y: y
        #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


> system.time(
+ AR.ox <- AltReg( ox, linked=T, trace=T ) )
```

```
iteration 1 criterion: 1
       alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   res
CO     0.911 0.988 1.861         74.419 74.417     1.000 0.974 3.371 3.502 2.292
pulse -1.039 1.014 1.860         74.422 74.419     1.027 1.000 3.460 3.595 3.958

iteration 2 criterion: 0.07508045
       alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   res
CO    -0.714 1.011 1.255         74.419 74.956      1.00  0.99 3.399 3.311 2.251
pulse -2.006 1.022 3.020         73.878 74.419      1.01  1.00 3.433 3.344 3.981

iteration 3 criterion: 0.0594666
       alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   res
CO    -2.363 1.035 1.215         74.419 75.433     1.000 1.005 3.425 3.173 2.211
pulse -2.971 1.030 3.082         73.412 74.419     0.995 1.000 3.407 3.156 4.002

iteration 4 criterion: 0.04281372
       alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   res
CO    -4.019 1.058 1.177         74.419 75.831     1.000 1.019 3.447 3.084 2.175
pulse -3.963 1.039 3.139         73.034 74.419     0.982 1.000 3.384 3.027 4.021

iteration 5 criterion: 0.02856943
       alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   res
CO    -5.668 1.081 1.143         74.419 76.145     1.000  1.03 3.466 3.031 2.145
pulse -5.009 1.049 3.186         72.744 74.419     0.971  1.00 3.365 2.943 4.036

iteration 6 criterion: 0.01820552
       alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   res
CO    -7.307 1.103 1.113         74.419 76.382     1.000 1.039 3.482 3.003 2.121
pulse -6.124 1.062 3.223         72.530 74.419     0.962 1.000 3.351 2.890 4.048
```

```
iteration 7 criterion: 0.01140264
       alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   res
CO    -8.936 1.126  1.09         74.419 76.556     1.000 1.046 3.493 2.989 2.102
pulse -7.314 1.076  3.25         72.377 74.419     0.956 1.000 3.340 2.858 4.057

iteration 8 criterion: 0.007169339
        alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   re
CO    -10.562 1.148 1.071         74.419 76.680     1.000 1.051 3.502 2.982 2.08
pulse  -8.576 1.092 3.269         72.269 74.419     0.951 1.000 3.331 2.837 4.06

iteration 9 criterion: 0.005074459
        alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   re
CO    -12.190 1.169 1.057         74.419 76.768     1.000 1.055 3.508 2.980 2.07
pulse  -9.904 1.109 3.282         72.193 74.419     0.948 1.000 3.325 2.824 4.06

iteration 10 criterion: 0.003705422
        alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   re
CO    -13.826 1.191 1.047         74.419 76.830     1.000 1.058 3.513 2.978 2.06
pulse -11.290 1.126 3.292         72.140 74.419     0.945 1.000 3.321 2.816 4.07

iteration 11 criterion: 0.002686236
        alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   re
CO    -15.476 1.213 1.039         74.419 76.873     1.000  1.06 3.516 2.978 2.06
pulse -12.727 1.145 3.298         72.104 74.419     0.944  1.00 3.318 2.810 4.07

iteration 12 criterion: 0.001930191
        alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   re
CO    -17.144 1.236 1.034         74.419 76.903     1.000 1.061 3.518 2.978 2.06
```

```
pulse -14.211 1.165 3.303         72.079 74.419     0.942 1.000 3.315 2.807 4.07

iteration 13 criterion: 0.001381194
        alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   re
CO    -18.834 1.258 1.030         74.419 76.924     1.000 1.062 3.520 2.978 2.05
pulse -15.736 1.185 3.306         72.061 74.419     0.941 1.000 3.314 2.804 4.07

iteration 14 criterion: 0.0009863462
        alpha  beta sigma Intercept: CO  pulse Slope: CO pulse   IxR   MxI   re
CO    -20.548 1.281 1.027         74.419 76.938     1.000 1.063 3.521 2.978 2.05
pulse -17.301 1.205 3.308         72.049 74.419     0.941 1.000 3.313 2.802 4.07

AltReg converged after  14 iterations
Last convergence criterion was  0.0009863462
   user  system elapsed
  12.84    0.00   12.90


> AR.ox
```

```
 Conversion between methods:
             alpha   beta sd.pred int(t-f) slope(t-f) sd(t-f)
To:   From:
CO    CO     0.000  1.000   2.906    0.000      0.000   2.906
      pulse -2.159  1.063   6.385   -2.093      0.061   6.190
pulse CO     2.031  0.941   6.007    2.093     -0.061   6.190
      pulse  0.000  1.000   5.769    0.000      0.000   5.769

 Variance components (sd):
        s.d.
Method    IxR   MxI   res
  CO    3.521 2.978 2.055
  pulse 3.313 2.802 4.079
```

Variance components

Bendix Carstensen

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Monday 9th September
ROeS 2013, Dornbirn, Austria
http://BendixCarstensen.com/MethComp/Dornbirn.2013

(Var-comp)

Variance components

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

Variance components must be reported on the scale of measurements.
3 variance components / random effects:

- a_{ir}: between replicates within item, ω^2
  $\beta_m\omega$ is the relevant quantity
  — essentially a nuisance parameter.
- c_{mi}: matrix effect τ_m^2
  $\beta_m\tau_m$ is the scaling to use.
- e_{mir}: measurement error, residual variation σ_m^2
  σ_m is on the correct scale.

Variance components - which scale

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

- Note that c_{mi} — the matrix effect — is multiplied by β_m.
- Only relevant for $M = 2$, where the random effect cannot be separated between methods.
- But formally must be on different scales.

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`.

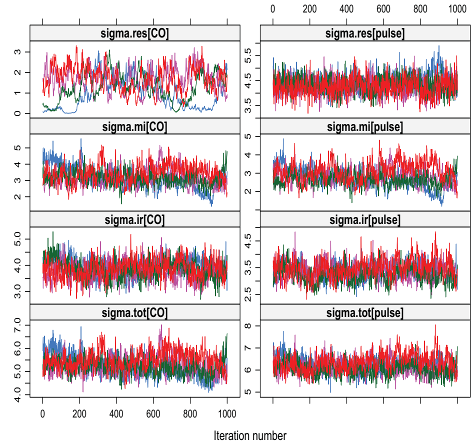
```
> options( width=61 )
> library(MethComp)
> data( ox )
> ox <- Meth( ox )

The following variables from the dataframe
"ox" are used as the Meth variables:
meth: meth
item: item
repl: repl
   y: y
        #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

> system.time( MCox <- MCmcmc( ox, IxR=TRUE, n.iter=10000 ) )
```

```
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
  pulse   1   4  56     61       177         24.0 75.0 94.0

Simulation run of a model with
- method by item and item by replicate interaction:
- using 4 chains run for 10000 iterations
  (of which 5000 are burn-in),
- monitoring every 5 values of the chain:
- giving a posterior sample of 4000 observations.

Initialization and burn-in:
Compiling model graph
   Resolving undeclared variables
   Allocating nodes
   Graph Size: 2868

Initializing model

Sampling:
   user  system elapsed
  66.36    0.04   66.59
```

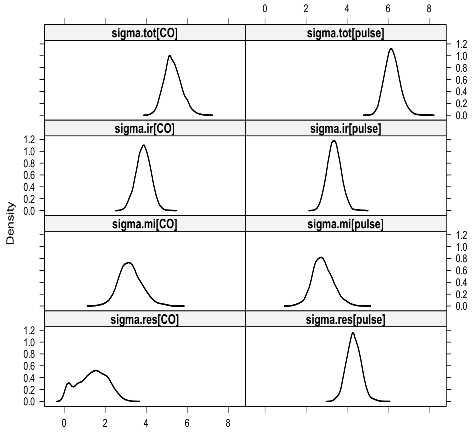
```
> MCox

 Conversion between methods:
                alpha   beta sd.pred int(t-f) slope(t-f) sd(t-f)
To:   From:
CO    CO       0.000  1.000   2.044    0.000      0.000   2.044
      pulse   -8.313  1.146   5.205   -7.748      0.136   4.851
pulse CO       7.254  0.873   4.540    7.748     -0.136   4.849
      pulse    0.000  1.000   6.105    0.000      0.000   6.105

 Variance components (sd):
      s.d.
Method     IxR   MxI   res
  CO    3.868 3.190 1.445
  pulse 3.368 2.783 4.317

Variance components with 95 % cred.int.:
    method    CO                pulse
    qnt       50%  2.5% 97.5%   50%  2.5% 97.5%
SD
IxR        3.868 3.142 4.557 3.368 2.744 4.043
MxI        3.190 2.214 4.454 2.783 1.898 3.904
res        1.445 0.114 2.653 4.317 3.645 5.037
tot        5.267 4.546 6.201 6.184 5.541 6.980

Mean parameters with 95 % cred.int.:
                   50%    2.5%  97.5% P(>0/1)
alpha[pulse.CO]  7.258  -1.332 14.891   0.946
alpha[CO.pulse] -8.309 -19.248  1.344   0.054
```

```
beta[pulse.CO]   0.873   0.772  0.988   0.012
beta[CO.pulse]   1.146   1.012  1.295   0.988

 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.

> post.MCmcmc( MCox )

> post.MCmcmc( MCox, check=FALSE )

> trace.MCmcmc( MCox )
```

Traces of the chains



Posteriors for variance components



Transformation of data

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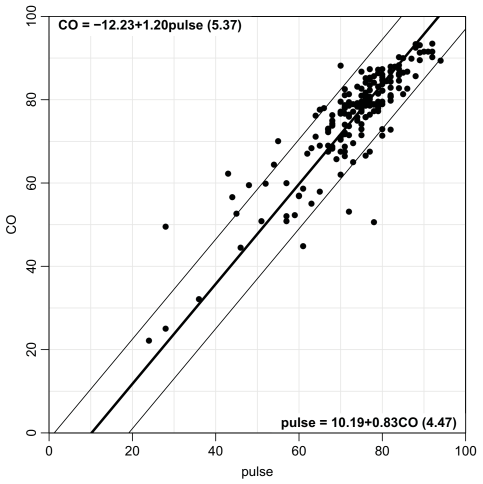
Monday 9th September
ROeS 2013, Dornbirn, Austria
http://BendixCarstensen.com/MethComp/Dornbirn.2013

(Transform)

If variances are not constant

A transformation might help:

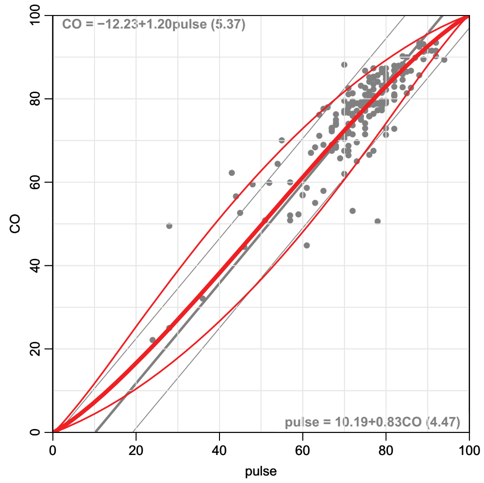
```
> round( ftable( DA.reg(ox) ), 3 )
                alpha   beta sd.pred beta=1 s.d.=K
From: To:
CO    CO        0.000  1.000      NA     NA     NA
      pulse     1.864  0.943   5.979  0.142  0.000
pulse CO       -1.977  1.061   6.342  0.142  0.000
      pulse     0.000  1.000      NA     NA    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



```
> library(MethComp)
> data( ox )
> ox <- Meth( ox )

The following variables from the dataframe
"ox" are used as the Meth variables:
meth: meth
item: item
repl: repl
   y: y
        #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

> system.time( MCox <- MCmcmc( ox, IxR=TRUE ) )
```

```
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
  pulse   1   4  56     61       177          24.0 75.0 94.0

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.

Initialization and burn-in:
Compiling model graph
   Resolving undeclared variables
   Allocating nodes
   Graph Size: 2868

Initializing model

Sampling:
   user  system elapsed
  14.35    0.07   16.97
```

```
> Mox <- MethComp( MCox )

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plot( Mox, points=TRUE, axlim=c(0,100), xaxs="i", yaxs="i" )

Relationships between methods:
 CO-pulse = -11.12+0.18(CO+pulse)/2 (4.88)
 CO = -12.23+1.20pulse (5.37)
 pulse = 10.19+0.83CO (4.47)
```

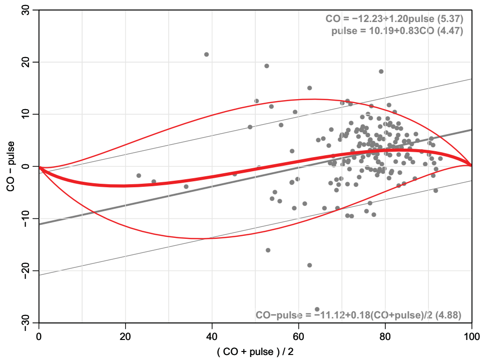


```
> system.time( MCox <- MCmcmc( ox, IxR=TRUE, Transform="pctlogit" ) )

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    -1.254049 1.300981 2.666159
  pulse   1   4  56     61       177    -1.152680 1.098612 2.751535

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.

Initialization and burn-in:
Compiling model graph
   Resolving undeclared variables
   Allocating nodes
   Graph Size: 2869

Initializing model
```

```
Sampling:
   user  system elapsed
  14.44    0.00   14.51

> Tox <- MethComp( MCox )

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plot( Mox, points=TRUE, axlim=c(0,100), xaxs="i", yaxs="i",
+       col.lines=gray(0.5), col.points=gray(0.5) )

Relationships between methods:
 CO-pulse = -11.12+0.18(CO+pulse)/2 (4.88)
 CO = -12.23+1.20pulse (5.37)
 pulse = 10.19+0.83CO (4.47)

> par( new=TRUE )
> plot( Tox, points=FALSE, axlim=c(0,100), xaxs="i", yaxs="i",
+       col.lines="red", lwd=c(5,2,2) )
```

Transformation to a Bland-Altman plot

Just convert to the differences versus the averages:



```
> system.time( MCox <- MCmcmc( ox, IxR=TRUE, Transform="pctlogit" ) )

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    -1.254049 1.300981 2.666159
  pulse   1   4  56     61       177    -1.152680 1.098612 2.751535

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.

Initialization and burn-in:
Compiling model graph
   Resolving undeclared variables
   Allocating nodes
   Graph Size: 2869

Initializing model
```

```
Sampling:
   user  system elapsed
  13.89    0.00   13.91

> Tox <- MethComp( MCox )
> Tox

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


 Conversion between methods:
              alpha   beta sd.pred int(t-f) slope(t-f) sd(t-f)
To:   From:
CO    CO      0.000  1.000   0.162    0.000      0.000   0.162
      pulse  -0.023  1.166   0.268   -0.021      0.153   0.247
pulse CO      0.020  0.858   0.231    0.021     -0.153   0.249
      pulse   0.000  1.000   0.293    0.000      0.000   0.293

 Variance components (sd):
       s.d.
Method    IxR   MxI   res
  CO    0.259 0.177 0.115
  pulse 0.222 0.153 0.207

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plot( Mox, pl.type="BA", points=TRUE, axlim=c(0,100), diflim=c(-30,30), xaxs="
```

```
Relationships between methods:
 CO-pulse = -11.12+0.18(CO+pulse)/2 (4.88)
 CO = -12.23+1.20pulse (5.37)
 pulse = 10.19+0.83CO (4.47)

> par( mar=c(3,3,1,1), mgp=c(3,1,0)/1.6 )
> plot( Mox, pl.type="BA", points=TRUE, axlim=c(0,100), diflim=c(-30,30), xaxs="
+       col.lines=gray(0.5), col.points=gray(0.5) )

Relationships between methods:
 CO-pulse = -11.12+0.18(CO+pulse)/2 (4.88)
 CO = -12.23+1.20pulse (5.37)
 pulse = 10.19+0.83CO (4.47)

> par( new=TRUE )
> plot( Tox, pl.type="BA", points=FALSE, axlim=c(0,100), diflim=c(-30,30), xaxs=
+       col.lines="red", lwd=c(5,2,2) )
```

Transformation of analysis

Note: estimates and variance components are on the logit-scale:

```
Note: Response transformed by:  function (p) log(p/(100 - p))

 Conversion between methods:
              alpha   beta sd.pred int(t-f) slope(t-f) sd(t-f)
To:   From:
CO    CO      0.000  1.000   0.162    0.000      0.000   0.162
      pulse  -0.025  1.167   0.270   -0.023      0.154   0.249
pulse CO      0.022  0.857   0.231    0.023     -0.154   0.249
      pulse   0.000  1.000   0.292    0.000      0.000   0.292

 Variance components (sd):
       s.d.
Method    IxR   MxI   res
  CO    0.259 0.174 0.114
  pulse 0.221 0.150 0.207
```

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