Overview of the package LMMstar

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This vignette describes the main functionalities of the **LMMstar** package. This package implements specific types of linear mixed models mainly useful when having repeated observations over a discrete variable (e.g. time, brain region, ...). Key assumptions are that at the cluster level, observation are independent and identically distributed and that the mean and variance are independent (conditionally on covariates). In particular, in large samples the residuals do not have to be normally distributed.

The **LMMstar** package contains four main functions:

- the function `lmm` is the main function of the package which fits linear mixed models. The user can interact with *lmm* objects using:
  - `anova` to test linear combinations of coefficients (Wald test or Likelihood ratio tests). Can be combined via `rbind`.
  - `coef` to extract the estimates.
  - `dummy.coef` to extract the estimated (marginal) mean for each combination of categorical covariate.
  - `estimate` to test non-linear combinations of coefficients (Wald test via a first order delta method).
  - `levels` to extract the reference level for the mean structure. (i.e. what `(Intercept)` refers to in presence of categorical. covariates).
  - `getVarCov` to extract the modeled residual variance covariance matrix.
  - `logLik` to output the log-likelihood of the estimated model.
  - `model.tables` to extract table containing estimates with the corresponding uncertainty.
  - `plot` to obtain a diagnostic plots, partial residual plots, or a graphical display of the fitted values.
  - `predict` to compute the conditional mean for new observations.
  - `residuals` to extract the observed residuals of the fitted model.
  - `summary` to obtain a summary of the input, model fit, and estimated values.
- the `summarize` function to compute summary statistics stratified on a categorical variable (typically time).
- the `sampleRem` function to simulate longitudinal data.
- the `LMMstar.options` function enables the user to display the default values used in the **LMMstar** package. The function can also change the default values to better match the user needs.

Before going further we need to load the **LMMstar** package in the R session:

```
library(LMMstar)
```

To illustrate the functionalities of the package, we will use the gastricbypass dataset:

```
data(gastricbypassL, package = "LMMstar")
head(gastricbypassL)
```

```
  id visit            time weight glucagonAUC
1  1     1 3 months before  127.2     5032.50
2  2     1 3 months before  165.2    12142.50
3  3     1 3 months before  109.7    10321.35
4  4     1 3 months before  146.2     6693.00
5  5     1 3 months before  113.1     7090.50
6  6     1 3 months before  158.8    10386.00
```

See `?gastricbypassL` for a presentation of the database. We will use a shorter version of the time variable:

```
gastricbypassL$time <- factor(gastricbypassL$time,
         levels = c("3 months before", "1 week before",
      "1 week after", "3 months after" ),
         labels = c("B3_months","B1_week","A1_week","A3_months"))
gastricbypassL$visit <- as.numeric(gastricbypassL$time) ## convert to numeric
gastricbypassL$baseline <- gastricbypassL$visit<=2
```

rescale the glucagon values

```
gastricbypassL$glucagon <- as.double(scale(gastricbypassL$glucagonAUC))+5
```

and add a group variable:

```
gastricbypassL$group <- as.numeric(gastricbypassL$id)%%2
```

Note: the **LMMstar** package is under active development. Newer package versions may include additional functionalities and fix previous bugs. The version of the package that is being used is:

```
utils::packageVersion("LMMstar")
```

```
[1] '0.5.3'
```

When estimating model coefficients, we will use the internal optimization routine of the **LMMstar** package (instead of relying on the `nlme::gls` function, which is the default option):

```
LMMstar.options(optimizer = "FS")
```

1 Descriptive statistics

Mean, standard deviation, and other summary statistic can be computed with respect to a categorical variable (typically time) using the `summarize` function:

```
sss <- summarize(weight+glucagon ~ time, data = gastricbypassL, na.rm = TRUE)
print(sss, digits = 3)
```

```
   outcome      time observed missing   mean     sd    min median    max
1   weight B3_months       20       0 128.97 20.269 100.90 123.10 173.00
2   weight   B1_week       20       0 121.24 18.910  95.70 114.50 162.20
3   weight   A1_week       20       0 115.70 18.275  89.90 110.60 155.00
4   weight A3_months       20       0 102.36 17.054  78.80  98.50 148.00
5 glucagon B3_months       20       0   4.51  0.641   3.61   4.33   6.03
6 glucagon   B1_week       19       1   4.39  0.558   3.58   4.23   5.95
7 glucagon   A1_week       19       1   6.06  1.044   4.52   5.94   8.27
8 glucagon A3_months       20       0   5.06  0.760   3.95   5.03   7.12
```

Correlation matrices are also ouput when a cluster and ordering variable have been specified (here respectively `id` and `time`):

```
sss <- summarize(weight ~ time|id, data = gastricbypassL, na.rm = TRUE)
print(sss, digits = 3)
```

```
  outcome      time observed missing mean   sd   min median max
1  weight B3_months       20       0  129 20.3 100.9  123.1 173
2  weight   B1_week       20       0  121 18.9  95.7  114.5 162
3  weight   A1_week       20       0  116 18.3  89.9  110.6 155
4  weight A3_months       20       0  102 17.1  78.8   98.5 148

 Pearson's correlation:
          B3_months B1_week A1_week A3_months
B3_months     1.000   0.990   0.986     0.946
B1_week       0.990   1.000   0.997     0.959
A1_week       0.986   0.997   1.000     0.966
A3_months     0.946   0.959   0.966     1.000
```

2 Linear mixed model

2.1 Covariance patterns

Fit a linear model with **identity** structure:

```
eId.lmm <- lmm(weight ~ time + glucagon,
        repetition = ~time|id, structure = "ID",
        data = gastricbypassL)
eId.lmm
cat(" covariance structure: \n");getVarCov(eId.lmm)
```

```
     Linear regression

 outcome/cluster/time: weight/id/time
 data                : 78 observations and distributed in 20 clusters
 parameters          : 5 mean ((Intercept) timeB1_week timeA1_week timeA3_months glucagon)
                       1 variance (sigma)
 log-restr.likelihood: -323.086426918519
 convergence         : TRUE (1 iterations)
 covariance structure:
          B3_months  B1_week  A1_week A3_months
B3_months  330.0427   0.0000   0.0000    0.0000
B1_week      0.0000 330.0427   0.0000    0.0000
A1_week      0.0000   0.0000 330.0427    0.0000
A3_months    0.0000   0.0000   0.0000  330.0427
```

Fit a linear model with **independence** structure:

```
eInd.lmm <- lmm(weight ~ time + glucagon,
        repetition = ~time|id, structure = "IND",
        data = gastricbypassL)
eInd.lmm
cat(" covariance structure: \n");getVarCov(eInd.lmm)
```

```
     Linear regression with heterogeneous residual variance

 outcome/cluster/time: weight/id/time
 data                : 78 observations and distributed in 20 clusters
 parameters          : 5 mean ((Intercept) timeB1_week timeA1_week timeA3_months glucagon)
                       4 variance (sigma k.B1_week k.A1_week k.A3_months)
 log-restr.likelihood: -321.457830361849
 convergence         : TRUE (9 iterations)
 covariance structure:
          B3_months  B1_week  A1_week A3_months
B3_months  442.6475   0.0000   0.0000    0.0000
B1_week      0.0000 418.9934   0.0000    0.0000
A1_week      0.0000   0.0000 222.8463    0.0000
A3_months    0.0000   0.0000   0.0000  237.2049
```

Fit a linear mixed model with **compound symmetry** structure:

```
eCS.lmm <- lmm(weight ~ time + glucagon,
        repetition = ~time|id, structure = "CS",
        data = gastricbypassL)
eCS.lmm
cat(" covariance structure: \n");getVarCov(eCS.lmm)
```

```
     Linear Mixed Model with a compound symmetry covariance matrix

 outcome/cluster/time: weight/id/time
 data                : 78 observations and distributed in 20 clusters
 parameters          : 5 mean ((Intercept) timeB1_week timeA1_week timeA3_months glucagon)
                       1 variance (sigma)
                       1 correlation (rho)
 log-restr.likelihood: -243.600523870253
 convergence         : TRUE (10 iterations)
 covariance structure:
          B3_months  B1_week  A1_week A3_months
B3_months  355.3062 344.6236 344.6236  344.6236
B1_week    344.6236 355.3062 344.6236  344.6236
A1_week    344.6236 344.6236 355.3062  344.6236
A3_months  344.6236 344.6236 344.6236  355.3062
```

Fit a linear mixed model with **stratified compound symmetry** covariance matrix:

```
eSCS.lmm <- lmm(weight ~ time*group,
  repetition = group~time|id, structure = "CS",
  data = gastricbypassL)
eSCS.lmm
cat(" covariance structure: \n");getVarCov(eSCS.lmm)
```

```
     Linear Mixed Model with a stratified compound symmetry covariance matrix

 outcome/cluster/time: weight/id/time
 data                : 80 observations and distributed in 20 clusters
 parameters          : 8 mean ((Intercept) timeB1_week timeA1_week timeA3_months group timeB1_week:
                       2 variance (sigma:0 sigma:1)
                       2 correlation (rho:0 rho:1)
 log-restr.likelihood: -233.141302306302
 convergence         : TRUE (7 iterations)
 covariance structure:
$`0`
           B3_months  B1_week  A1_week A3_months
B3_months  348.0783 334.7404 334.7404  334.7404
B1_week    334.7404 348.0783 334.7404  334.7404
A1_week    334.7404 334.7404 348.0783  334.7404
A3_months  334.7404 334.7404 334.7404  348.0783

$`1`
           B3_months  B1_week  A1_week A3_months
B3_months  345.1388 340.0877 340.0877  340.0877
B1_week    340.0877 345.1388 340.0877  340.0877
A1_week    340.0877 340.0877 345.1388  340.0877
A3_months  340.0877 340.0877 340.0877  345.1388
```

Fit a linear mixed model with **block compound symmetry** covariance matrix[1]:

```
eBCS.lmm <- lmm(weight ~ time*group,
  repetition = ~time|id, structure = CS(~baseline, heterogeneous = FALSE),
  data = gastricbypassL)
eBCS.lmm
cat(" covariance structure: \n");getVarCov(eBCS.lmm)
```

```
     Linear Mixed Model with a block compound symmetry covariance matrix

 outcome/cluster/time: weight/id/time
 data                : 80 observations and distributed in 20 clusters
 parameters          : 8 mean ((Intercept) timeB1_week timeA1_week timeA3_months group timeB1_week:
                       1 variance (sigma)
                       2 correlation (rho(TRUE,TRUE) rho(TRUE,FALSE))
 log-restr.likelihood: -234.971305082514
 convergence         : TRUE (7 iterations)
 covariance structure:
          B3_months  B1_week  A1_week A3_months
B3_months  346.6085 339.4747 336.3836  336.3836
B1_week    339.4747 346.6085 336.3836  336.3836
A1_week    336.3836 336.3836 346.6085  339.4747
A3_months  336.3836 336.3836 339.4747  346.6085
```

Fit a linear mixed model with **block unstructured** covariance matrix:

```
eBUN.lmm <- lmm(weight ~ time*group,
  repetition = ~time|id, structure = CS(~baseline),
  data = gastricbypassL)
eBUN.lmm
cat(" covariance structure: \n");getVarCov(eBUN.lmm)
```

```
     Linear Mixed Model with a block unstructured covariance matrix

 outcome/cluster/time: weight/id/time
 data                : 80 observations and distributed in 20 clusters
 parameters          : 8 mean ((Intercept) timeB1_week timeA1_week timeA3_months group timeB1_week:
                       2 variance (sigma k.TRUE)
                       3 correlation (rho(TRUE,TRUE) rho(TRUE,FALSE) rho(FALSE,FALSE))
 log-restr.likelihood: -231.80588606934
 convergence         : TRUE (7 iterations)
 covariance structure:
          B3_months  B1_week  A1_week A3_months
B3_months  377.4267 372.4602 336.3836  336.3836
B1_week    372.4602 377.4267 336.3836  336.3836
A1_week    336.3836 336.3836 315.7904  306.4892
A3_months  336.3836 336.3836 306.4892  315.7904
```

[1] same as nested random effects

Fit a linear mixed model with **unstructured** covariance matrix:

```
eUN.lmm <- lmm(weight ~ time + glucagon,
        repetition = ~time|id, structure = "UN",
        data = gastricbypassL)
eUN.lmm
cat(" covariance structure: \n");getVarCov(eUN.lmm)
```

```
     Linear Mixed Model with an unstructured covariance matrix

 outcome/cluster/time: weight/id/time
 data                : 78 observations and distributed in 20 clusters
 parameters          : 5 mean ((Intercept) timeB1_week timeA1_week timeA3_months glucagon)
                       4 variance (sigma k.B1_week k.A1_week k.A3_months)
                       6 correlation (rho(B3_months,B1_week) rho(B3_months,A1_week) rho(B3_months,A
 log-restr.likelihood: -216.318937004305
 convergence         : TRUE (23 iterations)
 covariance structure:
          B3_months  B1_week  A1_week A3_months
B3_months  411.3114 381.9734 352.6400  318.8573
B1_week    381.9734 362.7326 335.4649  304.6314
A1_week    352.6400 335.4649 311.6921  285.8077
A3_months  318.8573 304.6314 285.8077  280.9323
```

Fit a linear mixed model with **stratified unstructured** covariance matrix:

```
eSUN.lmm <- lmm(weight ~ time*group + glucagon,
  repetition = group~time|id, structure = "UN",
  data = gastricbypassL)
eSUN.lmm
cat(" covariance structure: \n");getVarCov(eSUN.lmm)
```

```
     Linear Mixed Model with a stratified unstructured covariance matrix

 outcome/cluster/time: weight/id/time
 data                : 78 observations and distributed in 20 clusters
 parameters          : 9 mean ((Intercept) timeB1_week timeA1_week timeA3_months group glucagon tim
                       8 variance (sigma:0 sigma:1 k.B1_week:0 k.A1_week:0 k.A3_months:0 k.B1_week:
                       12 correlation (rho(B3_months,B1_week):0 rho(B3_months,A1_week):0 rho(B3_mon
 log-restr.likelihood: -197.171312062212
 convergence         : TRUE (51 iterations)
 covariance structure:
$`0`
           B3_months  B1_week  A1_week A3_months
B3_months  417.3374 382.8829 362.5674  301.7430
B1_week    382.8829 364.4515 346.4039  292.7507
A1_week    362.5674 346.4039 331.1789  282.9301
A3_months  301.7430 292.7507 282.9301  253.3324

$`1`
           B3_months  B1_week  A1_week A3_months
B3_months  383.8877 363.6405 336.5771  350.0416
B1_week    363.6405 347.9898 321.5908  331.5182
A1_week    336.5771 321.5908 297.5329  308.1345
A3_months  350.0416 331.5182 308.1345  334.8267
```

2.2 Model output

The `summary` method can be used to display the main information relative to the model fit:

```
summary(eUN.lmm)
```

```
           Linear Mixed Model

Dataset: gastricbypassL

  - 20 clusters
  - 78 observations were analyzed, 2 were excluded because of missing values
  - between 3 and 4 observations per cluster

Summary of the outcome and covariates:

    $ weight  : num  127 165 110 146 113 ...
    $ time    : Factor w/ 4 levels "B3_months","B1_week",..: 1 1 1 1 1 1 1 1 1 1 ...
    $ glucagon: num  4.03 5.24 4.93 4.32 4.38 ...
    reference level: time=B3_months

Estimation procedure

  - Restricted Maximum Likelihood (REML)
  - log-likelihood :-216.3189
  - parameters: mean = 5, variance = 4, correlation = 6
  - convergence: TRUE (23 iterations)
    largest |score| = 7.034631e-05 for k.A1_week
            |change|= 1.097373342418e-06 for (Intercept)

Residual variance-covariance: unstructured

  - correlation structure: ~time
              B3_months B1_week A1_week A3_months
    B3_months     1.000   0.989   0.985     0.938
    B1_week       0.989   1.000   0.998     0.954
    A1_week       0.985   0.998   1.000     0.966
    A3_months     0.938   0.954   0.966     1.000

  - variance structure: ~time
              standard.deviation     ratio
    B3_months           20.28081 1.0000000
    B1_week             19.04554 0.9390916
    A1_week             17.65480 0.8705176
    A3_months           16.76104 0.8264480
```

```
Fixed effects: weight ~ time + glucagon

               estimate    se     df   lower   upper p.value
 (Intercept)     132.98 4.664 19.758 123.243 142.717 < 0.001 ***
 timeB1_week      -7.882 0.713 19.171  -9.374   -6.39 < 0.001 ***
 timeA1_week     -11.788 1.018 21.644   -13.9  -9.676 < 0.001 ***
 timeA3_months   -26.122 1.656  18.84 -29.591 -22.654 < 0.001 ***
 glucagon         -0.888 0.242 13.708  -1.408  -0.369 0.00257  **

 Uncertainty was quantified using model-based standard errors (column se).
 Degrees of freedom were computed using a Satterthwaite approximation (column df).
 The columns lower and upper indicate a 95% confidence interval for each coefficient.
```

Note: the calculation of the degrees of freedom, especially when using the observed information can be quite slow. Setting the arguments `df` to `FALSE` and `type.information` to `"expected"` when calling `lmm` should lead to a more reasonnable computation time.

2.3 Extract estimated coefficients

The value of the estimated coefficients can be output using `coef`:

```
coef(eUN.lmm)
```

```
(Intercept)   timeB1_week   timeA1_week timeA3_months      glucagon
132.9801355    -7.8822331   -11.7879545   -26.1223908    -0.8883081
```

Variance coefficients can be output by specifying the `effects` argument:

```
coef(eUN.lmm, effects = "variance")
```

```
     sigma   k.B1_week   k.A1_week k.A3_months
20.2808131   0.9390916   0.8705176   0.8264480
```

It is possible to apply specific transformation on the variance coefficients, for instance to obtain the residual variance relative to each outcome:

```
coef(eUN.lmm, effects = "variance", transform.k = "sd")
```

```
sigma:B3_months   sigma:B1_week   sigma:A1_week sigma:A3_months
       20.28081        19.04554        17.65480        16.76104
```

The marginal means at each timepoint can be obtained using `dummy.coef`:

```
dummy.coef(eUN.lmm)
```

```
       time estimate       se       df     lower    upper
1 B3_months 128.5386 4.536445 18.97584 119.04289 138.0343
2   B1_week 120.6564 4.261691 19.04078 111.73783 129.5749
3   A1_week 116.7506 3.956964 19.04925 108.47007 125.0312
4 A3_months 102.4162 3.747908 19.05531  94.57328 110.2591
```

2.4 Extract estimated coefficient and associated uncertainty

The uncertainty about the mean coefficients can be obtained using the `model.tables` method [2]:

```
model.tables(eUN.lmm)
```

```
             estimate    se   df  lower   upper  p.value
(Intercept)   132.980 4.664 19.8 123.24 142.717 0.00e+00
timeB1_week    -7.882 0.713 19.2  -9.37  -6.390 9.27e-10
timeA1_week   -11.788 1.018 21.6 -13.90  -9.676 9.55e-11
timeA3_months -26.122 1.656 18.8 -29.59 -22.654 2.62e-12
glucagon       -0.888 0.242 13.7  -1.41  -0.369 2.57e-03
```

Values for the all correlation parameters can be displayed too, by specifying `effect="all"`:

```
model.tables(eUN.lmm, effect = "all") ## not shown
```

Because these parameters are constrained (e.g. strictly positive), they uncertainty is by default computed after transformation (e.g. `log`) and then backtransformed.

2.5 Extract estimated residual variance-covariance structure

The method `getVarCov` can be used to output the covariance structure of the residuals:

```
getVarCov(eUN.lmm)
```

```
          B3_months  B1_week  A1_week A3_months
B3_months  411.3114 381.9734 352.6400  318.8573
B1_week    381.9734 362.7326 335.4649  304.6314
A1_week    352.6400 335.4649 311.6921  285.8077
A3_months  318.8573 304.6314 285.8077  280.9323
```

It can also be specific to a "known" individual:

```
getVarCov(eUN.lmm, individual = 5)
```

```
          B3_months  A1_week A3_months
B3_months  411.3114 352.6400  318.8573
A1_week    352.6400 311.6921  285.8077
A3_months  318.8573 285.8077  280.9323
```

or for a new individual:

```
newdata <- data.frame(id = "X", time = c("B3_months","B1_week","A1_week","A3_months"))
getVarCov(eUN.lmm, individual = newdata)
```

```
          B3_months  B1_week  A1_week A3_months
B3_months  411.3114 381.9734 352.6400  318.8573
B1_week    381.9734 362.7326 335.4649  304.6314
A1_week    352.6400 335.4649 311.6921  285.8077
A3_months  318.8573 304.6314 285.8077  280.9323
```

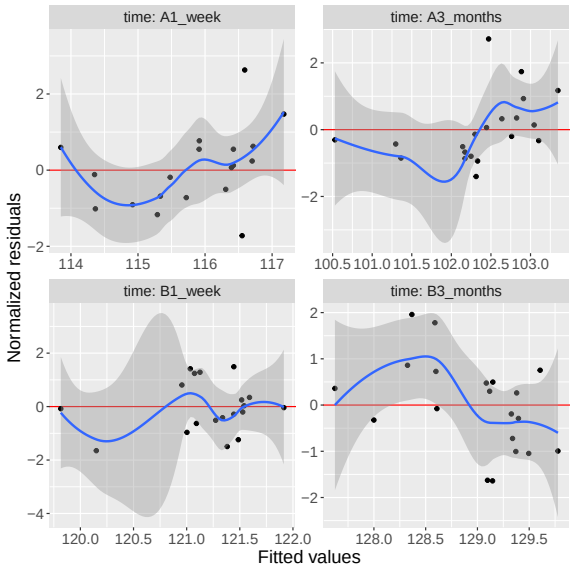
[2] it is equivalent to `confint` method except that by default it also outputs `se` and `p.value`

2.6 Model diagnostic

The method `plot` can be used to display diagnostic plots about:

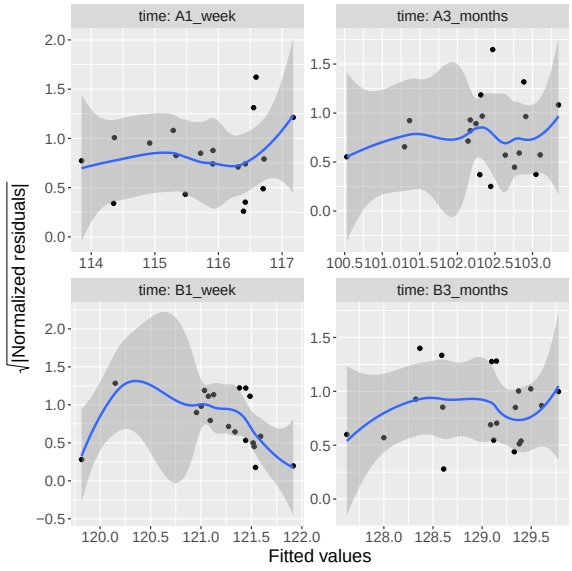
- misspecification of the mean structure

```
plot(eUN.lmm, type = "scatterplot")
```



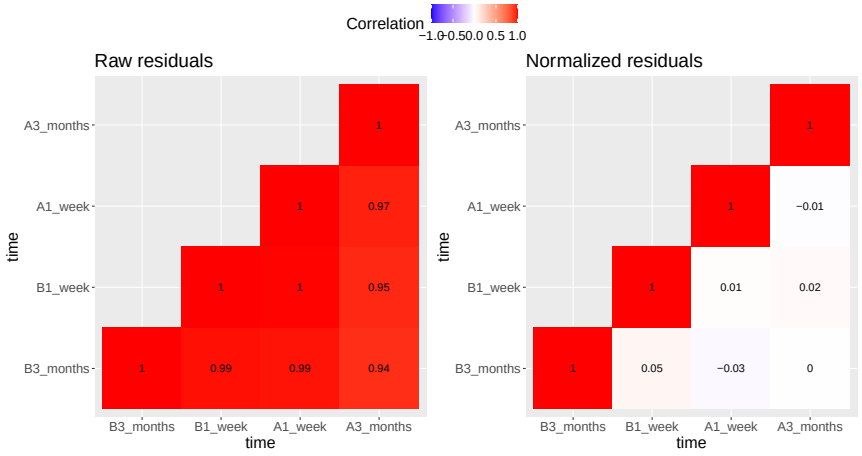
- misspecification of the variance structure

```
plot(eUN.lmm, type = "scatterplot2")
```



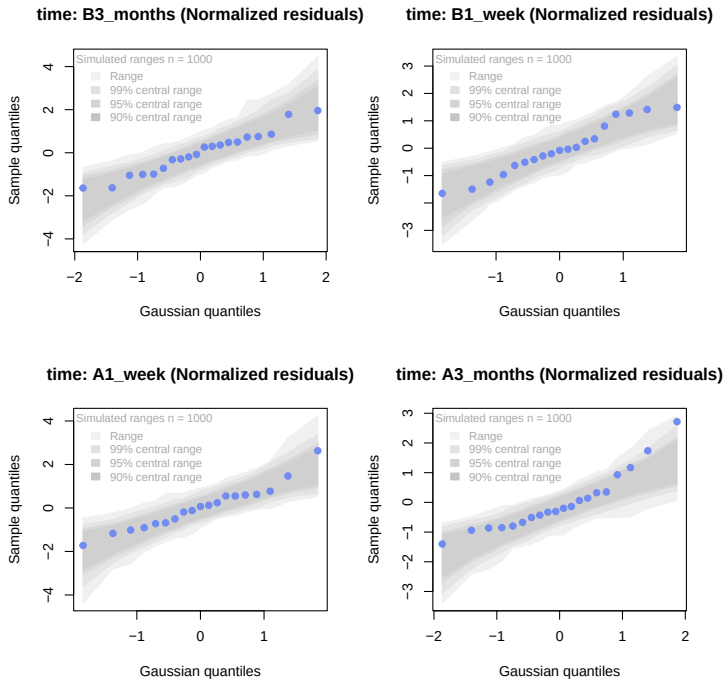
- misspecification of the correlation structure

```
plot(eUN.lmm, type = "correlation", type.residual = "response")
plot(eUN.lmm, type = "correlation", type.residual = "normalized")
```



- residual distribution vs. normal distribution [3]:

```
plot(eUN.lmm, type = "qqplot", engine.qqplot = "qqtest")
## Note: the qqtest package to be installed to use the argument engine.plot = "qqtest"
```



[3] see Oldford (2016) for guidance about how to read quantile-quantile plots.

The method `residuals` returns the residulas in the wide format:

```
eUN.diagW <- residuals(eUN.lmm, type = "normalized", format = "wide")
colnames(eUN.diagW) <- gsub("normalized.","",colnames(eUN.diagW))
head(eUN.diagW)
```

```
  cluster r.B3_months  r.B1_week   r.A1_week r.A3_months
1       1  -0.2897365 -0.2027622 -1.16864038   0.3258573
2       2   0.8603117 -1.6492164  0.62578801   1.7370660
3       3   0.7273066 -0.4155171 -0.68266741  -0.8510316
4       4  -1.6403082 -0.5128368  0.06806206   1.1725813
5       5   0.4755409         NA -0.18736415  -0.8634200
6       6   1.7801675  1.2847703  2.63004812   0.3505542
```

or in the long format:

```
eUN.diagL <- residuals(eUN.lmm, type = "normalized", format = "long")
head(eUN.diagL)
```

```
[1] -0.2897365  0.8603117  0.7273066 -1.6403082  0.4755409  1.7801675
```

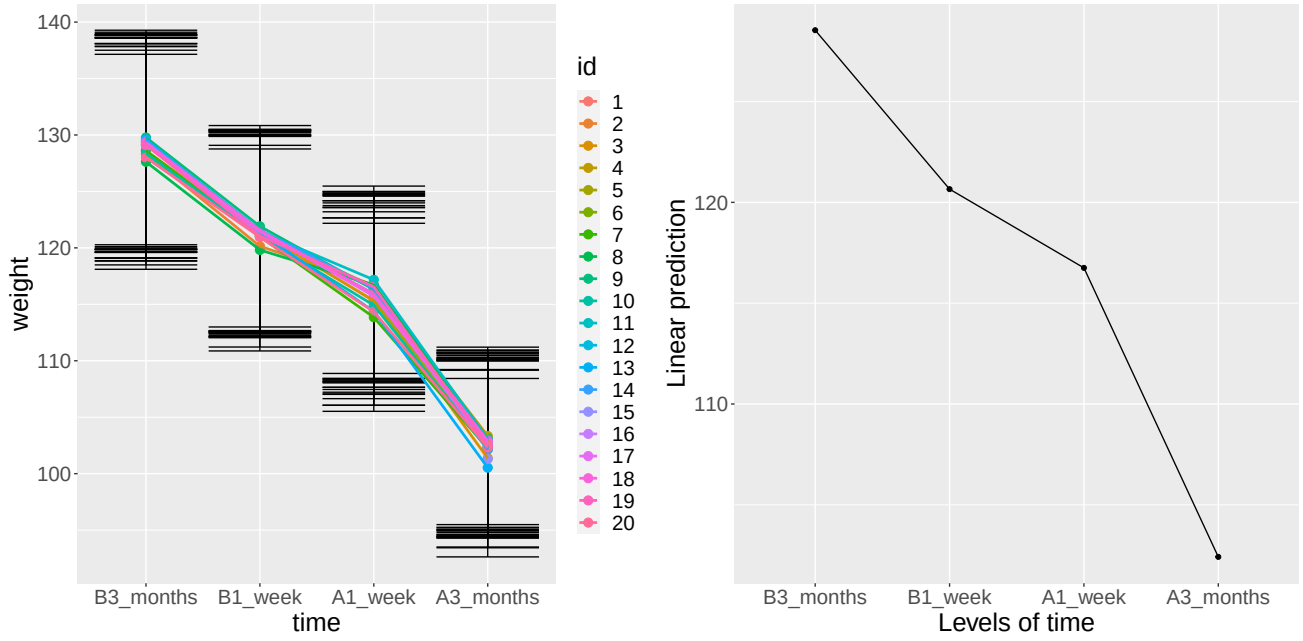
Various type of residuals can be extract but the normalized one are recommanded when doing model checking.

2.7 Model fit

The fitted values can be displayed via the `plot` method or using the `emmeans` package:

```
library(ggplot2) ## left panel
plot(eUN.lmm, type = "fit", color = "id", ci.alpha = NA, size.text = 20)
```

```
library(emmeans) ## right panel
emmip(eUN.lmm, ~time) + theme(text = element_text(size=20))
```

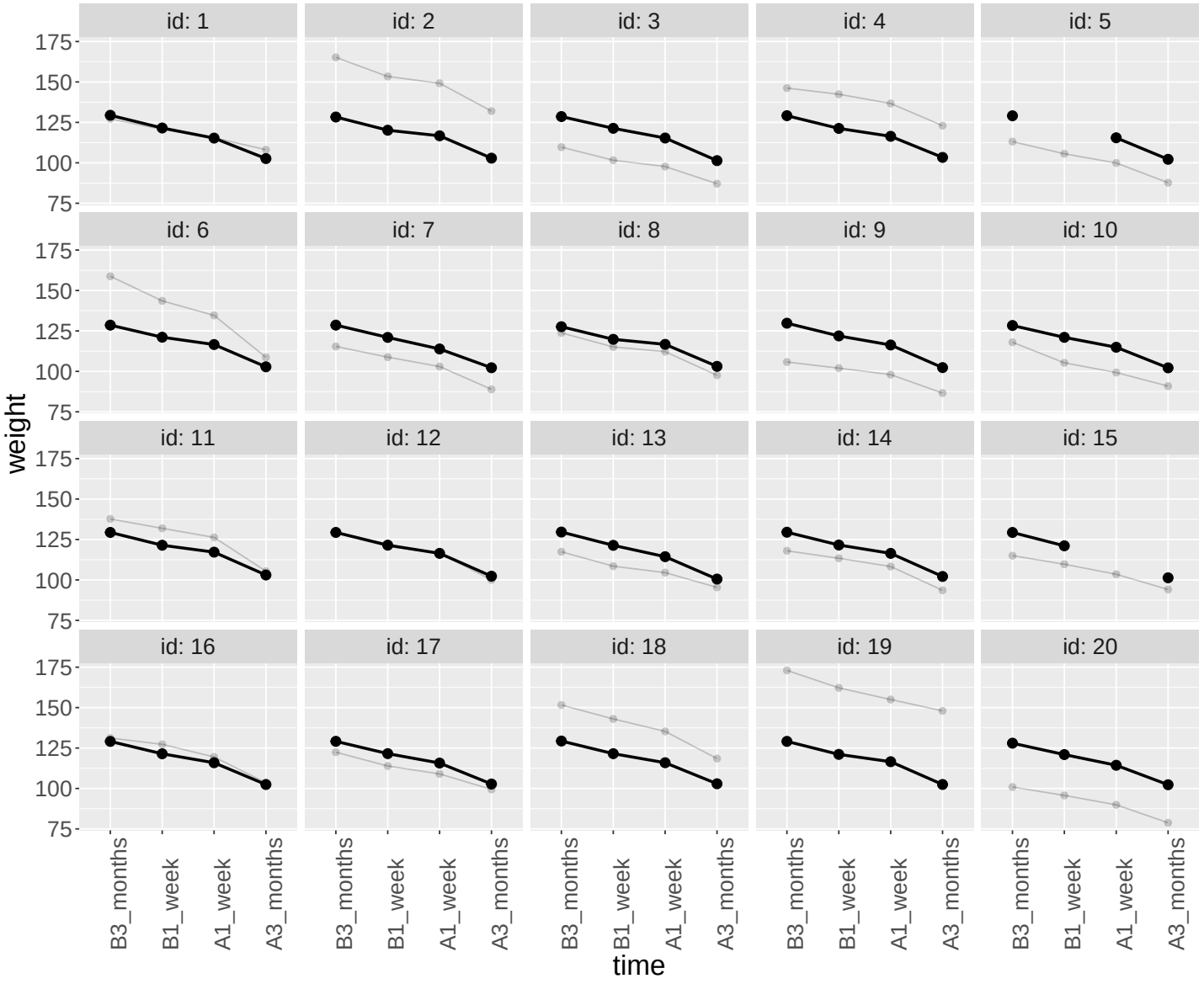


In the first case each possible curve is displayed while in the latter the average curve (over glucagon values). With the `plot` method, it is possible to display a curve specific to a glucagon value via the argument `at`:

```
plot(eUN.lmm, type = "fit", at = data.frame(glucagon = 10), color = "glucagon")
```

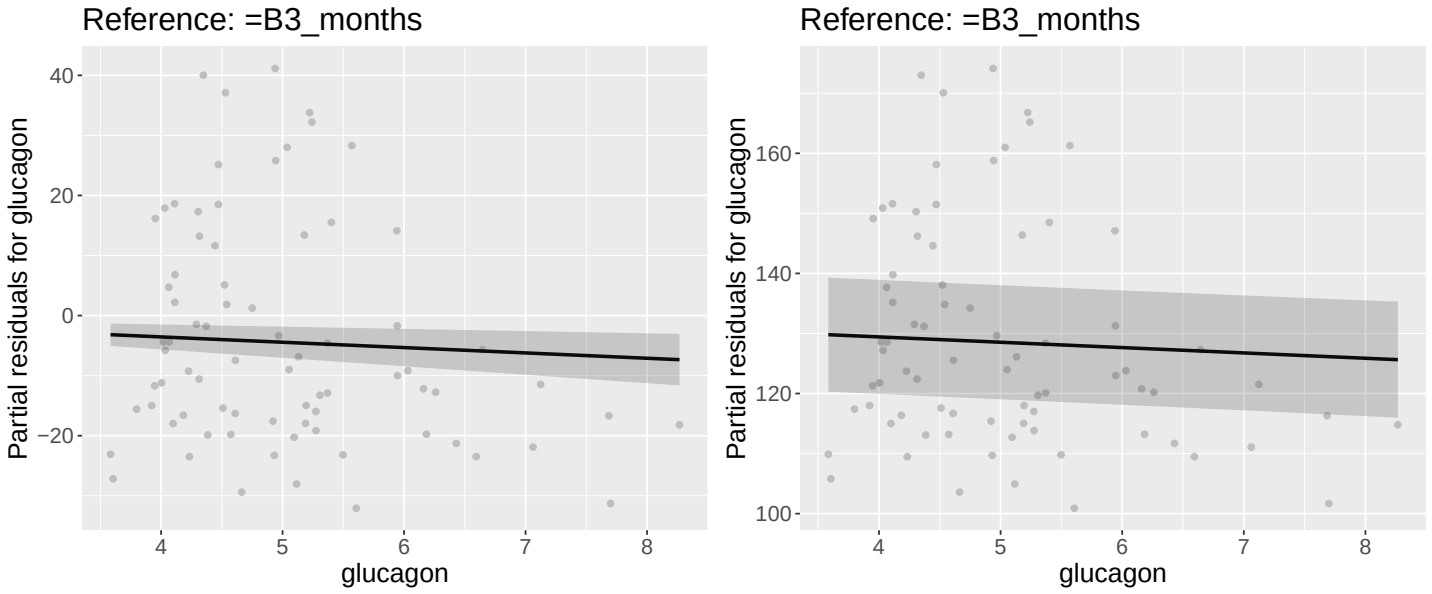
It is also possible to display the observed values along with the fitted values by setting the argument `obs.alpha` to a strictly positive value below or equal to 1. This argument controls the transparency of the color used to display the observed values:

```
gg <- plot(eUN.lmm, type = "fit", obs.alpha = 0.2, ci = FALSE,plot = FALSE)$plot
gg <- gg + facet_wrap(~id, labeller = label_both)
gg <- gg + theme(axis.text.x=element_text(angle = 90, hjust = 0))
gg
```



Partial residuals can also be displayed via the `plot` method:

```
gg1 <- plot(eUN.lmm, type = "partial", var = "glucagon", plot = FALSE)$plot
gg2 <- plot(eUN.lmm, type = "partial", var = c("(Intercept)","glucagon"), plot = FALSE)$plot
ggarrange(gg1,gg2)
```



Their value can be extracted via the `residuals` method, e.g.:

```
df.pres <- residuals(eUN.lmm, type = "partial", var = "glucagon", keep.data = TRUE)
m.pres <- gastricbypassL$weight - model.matrix(~time,gastricbypassL) %*% coef(eUN.lmm)[1:4]
range(df.pres$r.partial - m.pres, na.rm = TRUE)
```

```
[1] -1.065814e-14  1.154632e-14
```

2.8 Statistical inference (linear)

The anova method can be use to test one or several linear combinations of the model coefficients using Wald tests. By default, it will simultaneously test all parameters associated to a variable:

```
anova(eUN.lmm)
```

```
        || mean coefficients ||

 - Multivariate Wald test (global null hypothesis)
         statistic df.num df.denom    p.value
time        86.743      3   19.005 2.8424e-11 ***
glucagon    13.518      1   13.708  0.0025716  **
---
 Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Note that here the p-values are not adjust for multiple comparisons over variables. It is possible to specify a null hypothesis to be test: e.g. is there a change in average weight just after taking the treatment:

```
anova(eUN.lmm, effects = c("timeA1_week-timeB1_week=0"))
```

```
        || User-specified linear hypotheses ||

 - Multivariate Wald test (global null hypothesis)
 statistic df.num df.denom    p.value
    43.141      1   17.875 3.7234e-06 ***
---
 Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

One can also simulateneously tests several null hypotheses:

```
e.anova <- anova(eUN.lmm, effects = c("timeA1_week-timeB1_week=0",
          "timeA3_months-timeB1_week=0"))
summary(e.anova)
```

```
        || User-specified linear hypotheses ||

 - Multivariate Wald test (global null hypothesis)
 statistic df.num df.denom    p.value
    98.651      2    18.62 1.2338e-10 ***

 - Univariate Wald test (individual null hypotheses)
                             estimate        se        df     lower    upper p.value
timeA1_week - timeB1_week    -3.90572   0.59464  17.87453  -5.31903  -2.4924   2e-05 ***
timeA3_months - timeB1_week -18.24016   1.32283  19.02810 -21.38419 -15.0961  <1e-05 ***
```

```
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Standard errors: model-based
(CIs/p-values adjusted for multiple comparisons -- max-test adjustment)
CIs/p-values computed using 1e+05 samples.
```

or return all pairwise comparisons for a given factor using the `mcp` function of the multcomp package:

```
library(multcomp)
summary(anova(eUN.lmm, effects = mcp(time = "Tukey")))
```

```
Singular contrast matrix: contrasts "A1_week - B1_week" "A3_months - B1_week" "A3_months - A1_week"


        || User-specified linear hypotheses ||

 - Multivariate Wald test (global null hypothesis)
 statistic df.num df.denom    p.value
    86.743      3   19.005 2.8424e-11 ***

 - Univariate Wald test (individual null hypotheses)
                        estimate        se        df     lower    upper p.value
B1_week - B3_months    -7.88223   0.71318  19.17147  -9.81006  -5.9544  <1e-05 ***
A1_week - B3_months   -11.78795   1.01751  21.64404 -14.53843  -9.0375  <1e-05 ***
A3_months - B3_months -26.12239   1.65641  18.84049 -30.59989 -21.6449  <1e-05 ***
A1_week - B1_week      -3.90572   0.59464  17.87453  -5.51312  -2.2983   2e-05 ***
A3_months - B1_week   -18.24016   1.32283  19.02810 -21.81595 -14.6644  <1e-05 ***
A3_months - A1_week   -14.33444   1.05650  20.26658 -17.19030 -11.4786  <1e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Standard errors: model-based
(CIs/p-values adjusted for multiple comparisons -- max-test adjustment)
CIs/p-values computed using 1e+05 samples.
```

When testing transformed variance or correlation parameters, parentheses (as in `log(k).B1_week`) cause problem for recognizing parameters:

```
try(
  anova(eUN.lmm,
 effects = c("log(k).B1_week=0","log(k).A1_week=0","log(k).A3_months=0"))
)
```

```
Error in .anova_Wald(object, effects = effects, robust = robust, rhs = rhs,  :
  Possible mispecification of the argument 'effects' as running mulcomp::glht lead to the following
Error in parse(text = ex[i]) : <text>:1:7: uventet symbol
1: log(k).B1_week
          ^
```

It is then advised to build a contrast matrix, e.g.:

```
name.coef <- rownames(confint(eUN.lmm, effects = "all"))
name.varcoef <- grep("^k",name.coef, value = TRUE)
C <- matrix(0, nrow = 3, ncol = length(name.coef), dimnames = list(name.varcoef, name.coef))
diag(C[name.varcoef,name.varcoef]) <- 1
C
```

```
            (Intercept) timeB1_week timeA1_week timeA3_months glucagon sigma k.B1_week k.A1_week
k.B1_week             0           0           0             0        0     0         1         0
k.A1_week             0           0           0             0        0     0         0         1
k.A3_months           0           0           0             0        0     0         0         0
            k.A3_months rho(B3_months,B1_week) rho(B3_months,A1_week) rho(B3_months,A3_months)
k.B1_week             0                     0                     0                       0
k.A1_week             0                     0                     0                       0
k.A3_months           1                     0                     0                       0
            rho(B1_week,A1_week) rho(B1_week,A3_months) rho(A1_week,A3_months)
k.B1_week                      0                     0                     0
k.A1_week                      0                     0                     0
k.A3_months                    0                     0                     0
```

And then call the `anova` method specifying the null hypothesis via the contrast matrix:

```
anova(eUN.lmm, effects = C)
```

```
        || User-specified linear hypotheses ||

 - Multivariate Wald test (global null hypothesis)
 statistic df.num df.denom   p.value
    6.2032      3   17.995 0.0044171 **
---
 Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Note that using the approach of Pipper et al. (2012) it is also possible to adjust for multiple testing across several `lmm` objects. To do so, one first fit the mixed models, then use the `anova` method to indicate which hypotheses are being tested, and combine them using `rbind`.

Here is a (very artificial) example:

```
Manova <- rbind(anova(eInd.lmm, effects = "glucagon = 0"),
  anova(eCS.lmm, effects = "glucagon = 0"),
  anova(eUN.lmm, effects = "glucagon = 0"))
summary(Manova)
```

```
        || User-specified linear hypotheses ||

 - Multivariate Wald test (global null hypothesis)
 statistic df.num df.denom    p.value
    8.8925      3      Inf 6.8788e-06 ***

 - Univariate Wald test (individual null hypotheses)
      estimate        se        df     lower   upper p.value
[1,]  -8.27006   2.57880  34.20071 -14.88175 -1.6584 0.01173 *
[2,]   0.82179   0.61997  53.80983  -0.76772  2.4113 0.47205
[3,]  -0.88831   0.24161  13.70759  -1.50776 -0.2689 0.00399 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Standard errors: model-based
(CIs/p-values adjusted for multiple comparisons -- max-test adjustment)
CIs/p-values computed using 1e+05 samples.
```

2.9 Statistical inference (non-linear)

The `estimate` function can be used to test one or several non-linear combinations of model coefficients, using a first order delta method to quantify uncertainty. The combination has to be specified via a function (argument `f`). To illustrate its use consider an ANCOVA analysis:

$$Y_{i1} = \alpha + \beta Y_{i,0} + \gamma X_i + e_i$$

```
gastricbypassW <- reshape(gastricbypassL[,c("id","time","weight","group")],
     direction = "wide",
     timevar = "time", idvar = c("id","group"))
e.ANCOVA <- lm(weight.A1_week ~ weight.B1_week + group, data = gastricbypassW)
summary(e.ANCOVA)$coef
```

```
                Estimate Std. Error    t value     Pr(>|t|)
(Intercept)    -1.4823022 2.31781138 -0.6395267 5.310047e-01
weight.B1_week  0.9654917 0.01803988 53.5198489 2.156258e-20
group           0.2521714 0.66499945  0.3792054 7.092302e-01
```

We can replicate this analysis by first fitting a mixed model:

$$Y_{ij} = \alpha_j + \gamma_j X_i + \varepsilon_{i,j} \text{ where } \varepsilon_i \sim \mathcal{N}\left(\begin{bmatrix}0\\0\end{bmatrix}, \begin{bmatrix}\sigma_1^2 & \rho\sigma_1\sigma_2\\ \rho\sigma_1\sigma_2 & \sigma_2^2\end{bmatrix}\right)$$

```
e.lmmANCOVA <- lmm(weight ~ time+time:group, repetition = ~time|id,
     data = gastricbypassL[gastricbypassL$visit %in% 2:3,])
```

and then perform a delta-method:

```
lava::estimate(e.lmmANCOVA, f = function(p){
  c(Y1 = as.double(p["rho(B1_week,A1_week)"]*p["k.A1_week"]),
    X1 = as.double(p["timeA1_week:group"]-p["rho(B1_week,A1_week)"]*p["k.A1_week"]*p["timeB1_
    week:group"]))
})
```

```
    estimate         se       df      lower    upper   p.value
Y1 0.9654917 0.01753161 15.96769  0.9283203 1.002663 0.0000000
X1 0.2521714 0.64626331 15.00349 -1.1252784 1.629621 0.7018731
```

Indeed:

$$\begin{aligned}\mathbb{E}\left[Y_{i2}|Y_{i1}, X_i\right] &= \alpha_2 + \gamma_2 X_i + \rho\frac{\sigma_2}{\sigma_1}\left(Y_{i1} - \alpha_1 - \gamma_1 X_i\right)\\ &= \alpha_2 - \rho\frac{\sigma_2}{\sigma_1}\alpha_1 + \rho\frac{\sigma_2}{\sigma_1}Y_{i1} + \left(\gamma_2 - \rho\frac{\sigma_2}{\sigma_1}\gamma_1\right)X_i\end{aligned}$$

We obtain identical estimate but different standard-errors/degrees of freedom compared to the univariate linear model approach. The later is to be prefer as it does not rely on approximation. The former is nevertheless useful as it can handle missing data in the outcome variable.

2.10 Baseline adjustment

The `lmm` contains an "experimental" feature to drop non-identifiable effects from the model. For instance, let us define two (artifical) groups of patients:

```
gastricbypassL$group <- c("1","2")[as.numeric(gastricbypassL$id) %in% 15:20 + 1]
```

We would like to model group differences only after baseline (i.e. only at 1 week and 3 months after). For this we will define a treatment variable being the group variable except before baseline where it is "none":

```
gastricbypassL$treat <- baselineAdjustment(gastricbypassL, variable = "group",
        repetition = ~time|id, constrain = c("B3_months","B1_week"),
        new.level = "none")
table(treat = gastricbypassL$treat, time = gastricbypassL$time, group = gastricbypassL$group)
```

```
, , group = 1

      time
treat  B3_months B1_week A1_week A3_months
  none        14      14       0         0
  1            0       0      14        14
  2            0       0       0         0

, , group = 2

      time
treat  B3_months B1_week A1_week A3_months
  none         6       6       0         0
  1            0       0       0         0
  2            0       0       6         6
```

Here we will be able to estimate a total of 6 means and therefore can at most identify 6 effects. However the design matrix for the interaction model:

```
colnames(model.matrix(weight ~ treat*time, data = gastricbypassL))
```

```
[1] "(Intercept)"          "treat1"               "treat2"               "timeB1_week"
[5] "timeA1_week"          "timeA3_months"        "treat1:timeB1_week"   "treat2:timeB1_week"
[9] "treat1:timeA1_week"   "treat2:timeA1_week"   "treat1:timeA3_months" "treat2:timeA3_months"
```

contains 12 parameters (i.e. 6 too many). The `lmm` function will internally remove the one that cannot be identified and fit a simplified model:

```
eC.lmm <- lmm(weight ~ treat*time, data = gastricbypassL,
       repetition = ~time|id, structure = "UN")
```

```
Constant values in the design matrix in interactions "treat:time"
 Coefficients "treat1" "treat2" "timeA1_week" "timeA3_months" "treat1:timeB1_week" "treat2:timeB1_w
```

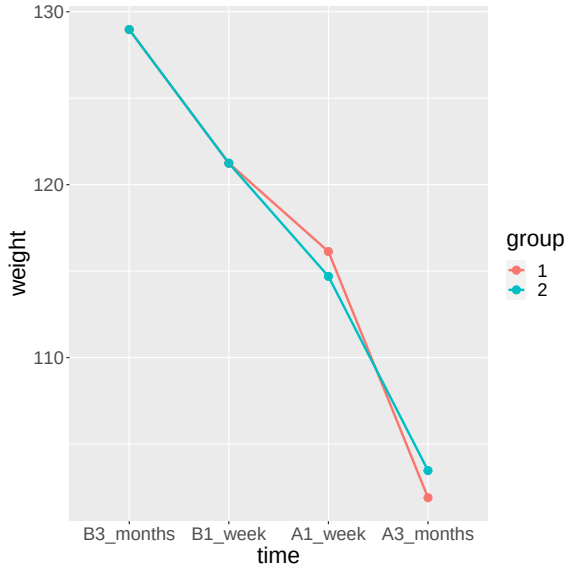
with the following coefficients:

```
coef(eC.lmm, effects = "mean")
```

```
         (Intercept)          timeB1_week   treat1:timeA1_week   treat2:timeA1_week
           128.97000             -7.73000            -12.83949            -14.27452
treat1:timeA3_months treat2:timeA3_months
           -27.07620            -25.50553
```

One can vizualize the baseline adjustment via the `autoplot` function:

```
autoplot(eC.lmm, color = "group", ci = FALSE, size.text = 20)
```



To more easily compare the two groups, one could set the baseline treatment to the treatment in the control arm by omitting the argument `new.level`:

```
gastricbypassL$treat2 <- baselineAdjustment(gastricbypassL, variable = "group",
         repetition = ~time|id, constrain = c("B3_months","B1_week"))
table(treat = gastricbypassL$treat2, time = gastricbypassL$time, group = gastricbypassL$group)
```

```
, , group = 1

     time
treat B3_months B1_week A1_week A3_months
    1        14      14      14        14
    2         0       0       0         0

, , group = 2

     time
treat B3_months B1_week A1_week A3_months
    1         6       6       0         0
    2         0       0       6         6
```

Fitting the model

```
eC2.lmm <- suppressWarnings(lmm(weight ~ treat2*time, data = gastricbypassL,
    repetition = ~time|id, structure = "UN"))
```

```
Constant values in the design matrix in interactions "treat2:time"
 Coefficients "treat22" "treat22:timeB1_week" have been removed.
```

will directly output group differences (last two coefficients):

```
model.tables(eC2.lmm)
```

```
                     estimate    se   df  lower  upper  p.value
(Intercept)            128.97 4.532 19.0 119.48 138.46 0.00e+00
timeB1_week             -7.73 0.697 19.0  -9.19  -6.27 1.00e-09
timeA1_week            -12.84 0.865 20.5 -14.64 -11.04 2.02e-12
timeA3_months          -27.08 1.724 21.4 -30.66 -23.50 3.20e-13
treat22:timeA1_week     -1.44 0.621 16.3  -2.75  -0.12 3.43e-02
treat22:timeA3_months    1.57 2.463 16.3  -3.64   6.78 5.32e-01
```

It is also possible to get the estimated mean at each timepoint, using an equivalent mean structure:

```
eC3.lmm <- suppressWarnings(lmm(weight ~ 0+treat2:time, data = gastricbypassL,
    repetition = ~time|id, structure = "UN"))
model.tables(eC3.lmm) ## equivalent to dummy.coef(eC2.lmm)
```

```
Constant values in the design matrix in interactions "treat2:time"
 Coefficients "treat22:timeB3_months" "treat22:timeB1_week" have been removed.
                     estimate   se   df lower upper p.value
treat21:timeB3_months      129 4.53 19.0 119.5   138       0
treat21:timeB1_week        121 4.23 19.0 112.4   130       0
treat21:timeA1_week        116 4.11 19.1 107.5   125       0
treat22:timeA1_week        115 4.13 19.4 106.1   123       0
treat21:timeA3_months      102 3.87 20.2  93.8   110       0
treat22:timeA3_months      103 4.17 25.2  94.9   112       0
```

or the baseline mean and the change since baseline:

```
eC4.lmm <- suppressWarnings(lmm(weight ~ treat2:time, data = gastricbypassL,
    repetition = ~time|id, structure = "UN"))
model.tables(eC4.lmm)
```

```
Constant values in the design matrix in interactions "treat2:time"
 Coefficients "treat22:timeB3_months" "treat22:timeB1_week" have been removed.
                     estimate    se   df  lower  upper  p.value
(Intercept)            128.97 4.532 19.0 119.48 138.46 0.00e+00
treat21:timeB1_week     -7.73 0.697 19.0  -9.19  -6.27 1.00e-09
treat21:timeA1_week    -12.84 0.865 20.5 -14.64 -11.04 2.02e-12
treat22:timeA1_week    -14.27 0.950 26.3 -16.23 -12.32 2.02e-14
treat21:timeA3_months  -27.08 1.724 21.4 -30.66 -23.50 3.20e-13
treat22:timeA3_months  -25.51 2.323 22.6 -30.32 -20.69 1.60e-10
```

2.11 Marginal means

The `emmeans` package can be used to output marginal means. Consider the following model:

```
e.group <- lmm(weight ~ time*group, data = gastricbypassL,
        repetition = ~time|id, structure = "UN")
```

We can for instance compute the average value over time *assuming balanced groups*:

```
emmeans(e.group, specs=~time)
```

```
NOTE: Results may be misleading due to involvement in interactions
 time       emmean   SE   df lower.CL upper.CL
 B3_months     130 5.05 18.0    119.3      141
 B1_week       122 4.69 18.0    112.5      132
 A1_week       117 4.55 18.0    107.0      126
 A3_months     104 4.20 18.1     94.9      113

Results are averaged over the levels of: group
Confidence level used: 0.95
```

This differs from the average value over time over the whole sample:

```
df.pred <- cbind(gastricbypassL, predict(e.group, newdata = gastricbypassL))
summarize(formula = estimate~time, data = df.pred)
```

```
   outcome      time observed missing    mean       sd      min   median    max
1 estimate B3_months       20       0 128.970 2.270212 127.5214 127.5214 132.35
2 estimate   B1_week       20       0 121.240 2.726942 119.5000 119.5000 125.30
3 estimate   A1_week       20       0 115.700 2.014981 114.4143 114.4143 118.70
4 estimate A3_months       20       0 102.365 3.146729 100.3571 100.3571 107.05
```

as the groups are not balanced:

```
table(group = gastricbypassL$group, time = gastricbypassL$time)
```

```
     time
group B3_months B1_week A1_week A3_months
    1        14      14      14        14
    2         6       6       6         6
```

The "emmeans" approach gives equal "weight" to the expected value of both group 2:

```
mu.group1 <-  as.double(coef(e.group)["(Intercept)"])
mu.group2 <-  as.double(coef(e.group)["(Intercept)"] + coef(e.group)["group2"])
p.group1 <- 14/20          ; p.group2 <- 6/20
c(emmeans = (mu.group1+mu.group2)/2, predict = mu.group1 * p.group1 + mu.group2 * p.group2)
```

```
 emmeans  predict
129.9357 128.9700
```

Which one is relevant depends on the application. The `emmeans` function can also be used to display expected value in each group over time:

```
emmeans.group <- emmeans(e.group, specs = ~group|time)
emmeans.group
```

```
time = B3_months:
 group emmean   SE   df lower.CL upper.CL
 1        128 5.53 18.0    115.9      139
 2        132 8.45 18.0    114.6      150

time = B1_week:
 group emmean   SE   df lower.CL upper.CL
 1        120 5.14 18.0    108.7      130
 2        125 7.85 18.0    108.8      142

time = A1_week:
 group emmean   SE   df lower.CL upper.CL
 1        114 4.99 18.0    103.9      125
 2        119 7.62 18.0    102.7      135

time = A3_months:
 group emmean   SE   df lower.CL upper.CL
 1        100 4.60 18.1     90.7      110
 2        107 7.03 18.1     92.3      122

Confidence level used: 0.95
```

Using the `pair` function displays the differences:

```
epairs.group <- pairs(emmeans.group, reverse = TRUE)
epairs.group
```

```
time = B3_months:
 contrast estimate    SE   df t.ratio p.value
 2 - 1        4.83 10.10 18.0   0.478  0.6383

time = B1_week:
 contrast estimate    SE   df t.ratio p.value
 2 - 1        5.80  9.38 18.0   0.618  0.5441

time = A1_week:
 contrast estimate    SE   df t.ratio p.value
 2 - 1        4.29  9.11 18.0   0.471  0.6435

time = A3_months:
 contrast estimate    SE   df t.ratio p.value
 2 - 1        6.69  8.40 18.1   0.797  0.4361
```

One can adjust for multiple comparison via the `adjust` argument and display confidence intervals setting the argument `infer` to `TRUE`:

```
summary(epairs.group, by = NULL, adjust = "mvt", infer = TRUE)
```

```
 contrast time       estimate    SE   df lower.CL upper.CL t.ratio p.value
 2 - 1    B3_months     4.83 10.10 18.0    -18.0     27.7   0.478  0.7496
 2 - 1    B1_week       5.80  9.38 18.0    -15.4     27.0   0.618  0.6481
 2 - 1    A1_week       4.29  9.11 18.0    -16.3     24.9   0.471  0.7551
 2 - 1    A3_months     6.69  8.40 18.1    -12.3     25.7   0.797  0.5285

Confidence level used: 0.95
Conf-level adjustment: mvt method for 4 estimates
P value adjustment: mvt method for 4 tests
```

This should also work when doing baseline adjustment (because of baseline adjustment no difference is expected at the first two timepoints):

```
summary(pairs(emmeans(eC2.lmm , specs = ~treat2|time), reverse = TRUE), by = NULL)
```

```
Note: adjust = "tukey" was changed to "sidak"
because "tukey" is only appropriate for one set of pairwise comparisons
 contrast time       estimate    SE   df t.ratio p.value
 2 - 1    B3_months     0.00 0.000  NaN     NaN     NaN
 2 - 1    B1_week       0.00 0.000  NaN     NaN     NaN
 2 - 1    A1_week      -1.44 0.621 16.2  -2.311  0.1303
 2 - 1    A3_months     1.57 2.463 16.3   0.638  0.9522

P value adjustment: sidak method for 4 tests
```

2.12 Predictions

Two types of predictions can be performed with the `predict` method:

- **static predictions** that are only conditional on the covariates:

```
news <- gastricbypassL[gastricbypassL$id==1,]
news$glucagon <- 0
predict(eUN.lmm, newdata = news)
```

```
  estimate       se       df     lower    upper
1 132.9801 4.664247 19.75815 123.24305 142.7172
2 125.0979 4.388294 19.91418 115.94155 134.2543
3 121.1922 4.214230 20.55331 112.41660 129.9678
4 106.8577 3.942058 20.95499  98.65871 115.0568
```

which can be computing by creating a design matrix:

```
X.12 <- model.matrix(formula(eUN.lmm), news)
X.12
```

```
   (Intercept) timeB1_week timeA1_week timeA3_months glucagon
1            1           0           0             0        0
21           1           1           0             0        0
41           1           0           1             0        0
61           1           0           0             1        0
attr(,"assign")
[1] 0 1 1 1 2
attr(,"contrasts")
attr(,"contrasts")$time
[1] "contr.treatment"
```

and then multiplying it with the regression coefficients:

```
X.12 %*% coef(eUN.lmm)
```

```
       [,1]
1  132.9801
21 125.0979
41 121.1922
61 106.8577
```

- **dynamic predictions** that are conditional on the covariates and the outcome measured at other timepoints. Consider two subjects for who we would like to predict the weight 1 week before the intervention based on the weight 3 months before the intervention:

```
newd <- rbind(
  data.frame(id = 1, time = "B3_months", weight = coef(eUN.lmm)["(Intercept)"], glucagon = 0),
  data.frame(id = 1, time = "B1_week", weight = NA, glucagon = 0),
  data.frame(id = 2, time = "B3_months", weight = 100, glucagon = 0),
  data.frame(id = 2, time = "B1_week", weight = NA, glucagon = 0)
)
predict(eUN.lmm, newdata = newd, type = "dynamic", keep.newdata = TRUE)
```

```
  id      time   weight glucagon  estimate        se  df     lower    upper
1  1 B3_months 132.9801        0        NA        NA  NA        NA       NA
2  1   B1_week       NA        0 125.09790 0.6362754 Inf 123.85083 126.3450
3  2 B3_months 100.0000        0        NA        NA  NA        NA       NA
4  2   B1_week       NA        0  94.47017 7.2279385 Inf  80.30367 108.6367
```

The first subjects has the average weight while the second has a much lower weight. The predicted weight for the first subject is then the average weight one week before while it is lower for the second subject due to the positive correlation over time. The predicted value is computed using the formula of the conditional mean for a Gaussian vector:

```
mu1 <- coef(eUN.lmm)[1]
mu2 <- sum(coef(eUN.lmm)[1:2])
Omega_11 <- getVarCov(eUN.lmm)["B3_months","B3_months"]
Omega_21 <- getVarCov(eUN.lmm)["B1_week","B3_months"]
as.double(mu2 + Omega_21 * (100 - mu1) / Omega_11)
```

```
[1] 94.47017
```

2.13 Missing values and imputation

We now consider the glucagon level as an outcome. The `summarize` function can be used to describe the amount of missing data at each repetition:

```
sss <- summarize(glucagon ~ time, data = gastricbypassL, na.rm = TRUE)
cbind(sss[,1:4], pc = paste0(100 * sss$missing / (sss$missing + sss$observed), "%"))
```

```
   outcome      time observed missing pc
1 glucagon B3_months       20       0 0%
2 glucagon   B1_week       19       1 5%
3 glucagon   A1_week       19       1 5%
4 glucagon A3_months       20       0 0%
```

Further description of the missing data patterns rely on function outside the LMMstar package, e.g. appropriate call to `tapply` and `table`:

```
vec.pattern <- tapply(as.numeric(is.na(gastricbypassL$glucagon)),
        INDEX = gastricbypassL$id,
        FUN = paste, collapse=".")
table(vec.pattern)
```

```
vec.pattern
0.0.0.0 0.0.1.0 0.1.0.0
     18       1       1
```

Linear mixed model can handle missing value in the outcome variable, assuming that missigness is random conditional on the covariate and observed outcome values. The `lmm` function can be used "as usual":

```
eUN.lmmNA <- lmm(glucagon ~ time,
   repetition = ~time|id, structure = "UN",
   data = gastricbypassL)
summary(eUN.lmmNA, hide.fit = TRUE,
 hide.cor = TRUE, hide.sd = TRUE, hide.mean = TRUE)
```

```
           Linear Mixed Model

Dataset: gastricbypassL

  - 20 clusters
  - 78 observations were analyzed, 2 were excluded because of missing values
  - between 3 and 4 observations per cluster

Summary of the outcome and covariates:

    $ glucagon: num  4.03 5.24 4.93 4.32 4.38 ...
    $ time    : Factor w/ 4 levels "B3_months","B1_week",..: 1 1 1 1 1 1 1 1 1 1 ...
    reference level: time=B3_months
```

The visible difference in the summary is when describing the dataset: we can see that some repetitions (here 2) have been ignored as the outcome was missing. So for some clusters only 3 values were analyzed instead of 4. It is possible to extract the most likely value for these missing observation using the `fitted` function with argument `impute=TRUE`:

```
fitted(eUN.lmmNA, impute = TRUE)
```

```
[1] 4.256984 6.497856
```

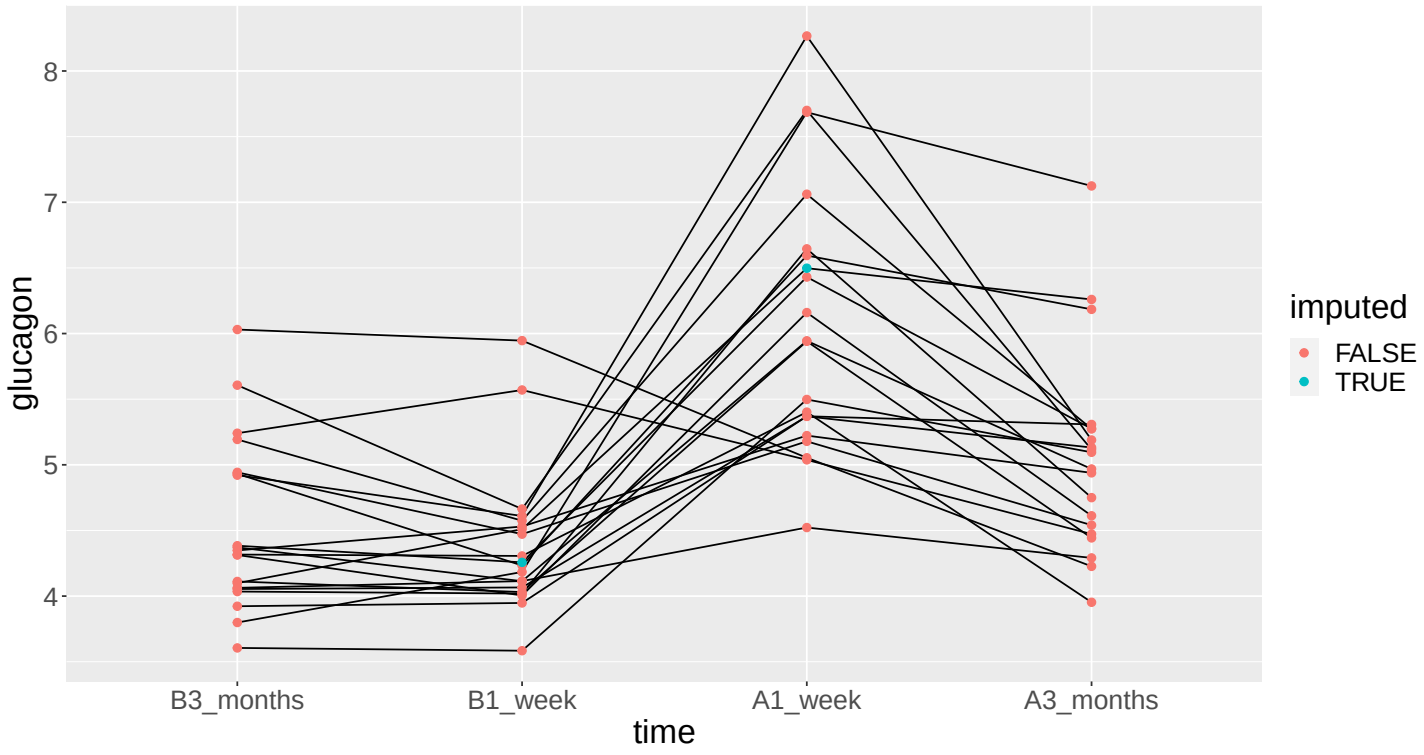
When using the argument `keep.newdata=TRUE`, the missing outcome value has been replaced by its most likely value (which is the same as the dynamic prediction, describedy previously):

```
eData <- fitted(eUN.lmmNA, impute = TRUE, keep.newdata = TRUE)
eData[eData$id %in% eData[eData$imputed,"id"],]
```

```
   id visit      time weight glucagon baseline group treat treat2 imputed estimate
5   5     1 B3_months  113.1 4.383738     TRUE     1  none      1   FALSE 4.514352
15 15     1 B3_months  115.0 4.098741     TRUE     2  none      1   FALSE 4.514352
25  5     2   B1_week  105.6 4.256984     TRUE     1  none      1    TRUE 4.386762
35 15     2   B1_week  109.7 4.509697     TRUE     2  none      1   FALSE 4.386762
45  5     3   A1_week   99.9 6.430376    FALSE     1     1      1   FALSE 6.078985
55 15     3   A1_week  103.5 6.497856    FALSE     2     2      2    TRUE 6.078985
65  5     4 A3_months   87.7 5.275118    FALSE     1     1      1   FALSE 5.057642
75 15     4 A3_months   94.1 6.259632    FALSE     2     2      2   FALSE 5.057642
```

Visually:

```
ggplot(eData, aes(x=time,y=glucagon, group=id)) + geom_line() + geom_point(aes(color=imputed))
```



It is possible to sample from the estimated distribution of the missing value instead of using the most likely value, e.g. accounting for residual variance and uncertainty related to parameter estimation:

```
set.seed(10)
fitted(eUN.lmmNA, impute = TRUE, se = "total")
fitted(eUN.lmmNA, impute = TRUE, se = "total")
fitted(eUN.lmmNA, impute = TRUE, se = "total")
```

```
[1] 4.262434 6.305287
[1] 3.858267 5.871642
[1] 4.342624 6.905246
```

3 Data generation

Simulate some data in the wide format:

```
set.seed(10) ## ensure reproductibility
n.obs <- 100
n.times <- 4
mu <- rep(0,4)
gamma <- matrix(0, nrow = n.times, ncol = 10) ## add interaction
gamma[,6] <- c(0,1,1.5,1.5)
dW <- sampleRem(n.obs, n.times = n.times, mu = mu, gamma = gamma, format = "wide")
head(round(dW,3))
```

```
  id X1 X2 X3 X4 X5     X6     X7     X8    X9    X10     Y1     Y2     Y3     Y4
1  1  1  0  1  1  0 -0.367  1.534 -1.894 1.729  0.959  1.791  2.429  3.958  2.991
2  2  1  0  1  2  0 -0.410  2.065  1.766 0.761 -0.563  2.500  4.272  3.002  2.019
3  3  0  0  2  1  0 -1.720 -0.178  2.357 1.966  1.215 -3.208 -5.908 -4.277 -5.154
4  4  0  0  0  1  0  0.923 -2.089  0.233 1.307 -0.906 -2.062  0.397  1.757 -1.380
5  5  0  0  2  1  0  0.987  5.880  0.385 0.028  0.820  7.963  7.870  7.388  8.609
6  6  0  0  1  1  2 -1.075  0.479  2.202 0.900 -0.739  0.109 -1.602 -1.496 -1.841
```

Simulate some data in the long format:

```
set.seed(10) ## ensure reproductibility
dL <- sampleRem(n.obs, n.times = n.times, mu = mu, gamma = gamma, format = "long")
head(dL)
```

```
  id visit        Y X1 X2 X3 X4 X5         X6       X7        X8        X9        X10
1  1     1 1.791444  1  0  1  1  0 -0.3665251 1.533815 -1.894425 1.7288665  0.9592499
2  1     2 2.428570  1  0  1  1  0 -0.3665251 1.533815 -1.894425 1.7288665  0.9592499
3  1     3 3.958350  1  0  1  1  0 -0.3665251 1.533815 -1.894425 1.7288665  0.9592499
4  1     4 2.991198  1  0  1  1  0 -0.3665251 1.533815 -1.894425 1.7288665  0.9592499
5  2     1 2.500179  1  0  1  2  0 -0.4097541 2.065413  1.765841 0.7613348 -0.5630173
6  2     2 4.272357  1  0  1  2  0 -0.4097541 2.065413  1.765841 0.7613348 -0.5630173
```

4 Modifying default options

The `LMMstar.options` method enable to get and set the default options used by the package. For instance, the default option for the information matrix is:

```
LMMstar.options("type.information")
```

```
$type.information
[1] "observed"
```

To change the default option to "expected" (faster to compute but less accurate p-values and confidence intervals in small samples) use:

```
LMMstar.options(type.information = "expected")
```

To restore the original default options do:

```
LMMstar.options(reinitialise = TRUE)
```

5 R session

Details of the R session used to generate this document:

```
sessionInfo()
```

```
R version 4.1.1 (2021-08-10)
Platform: x86_64-w64-mingw32/x64 (64-bit)
Running under: Windows 10 x64 (build 19044)

Matrix products: default

locale:
[1] LC_COLLATE=Danish_Denmark.1252  LC_CTYPE=Danish_Denmark.1252    LC_MONETARY=Danish_Denmark.1252
[4] LC_NUMERIC=C                    LC_TIME=Danish_Denmark.1252

attached base packages:
[1] stats     graphics  grDevices utils     datasets  methods   base

other attached packages:
 [1] lme4_1.1-27.1   Matrix_1.4-0    LMMstar_0.5.0   nlme_3.1-153    ggpubr_0.4.0    multcomp_1.4-1
 [7] TH.data_1.1-0   MASS_7.3-54     survival_3.2-13 mvtnorm_1.1-3   qqtest_1.2.0    emmeans_1.7.2
[13] ggplot2_3.3.5

loaded via a namespace (and not attached):
 [1] Rcpp_1.0.8          lattice_0.20-45     tidyr_1.1.4         listenv_0.8.0
 [5] zoo_1.8-9           assertthat_0.2.1    digest_0.6.29       utf8_1.2.2
 [9] parallelly_1.30.0   R6_2.5.1            plyr_1.8.6          backports_1.4.1
[13] coda_0.19-4         pillar_1.6.5        rlang_0.4.12        minqa_1.2.4
[17] nloptr_1.2.2.3      car_3.0-12          textshaping_0.3.6   labeling_0.4.2
[21] splines_4.1.1       stringr_1.4.0       munsell_0.5.0       broom_0.7.11
[25] compiler_4.1.1      numDeriv_2016.8-1.1 systemfonts_1.0.3   pkgconfig_2.0.3
[29] mgcv_1.8-38         globals_0.14.0      tidyselect_1.1.1    gridExtra_2.3
[33] tibble_3.1.6        codetools_0.2-18    fansi_1.0.2         future_1.23.0
[37] crayon_1.4.2        dplyr_1.0.7         withr_2.4.3         grid_4.1.1
[41] xtable_1.8-4        gtable_0.3.0        lifecycle_1.0.1     DBI_1.1.2
[45] magrittr_2.0.1      scales_1.1.1        estimability_1.3    future.apply_1.8.1
[49] stringi_1.7.6       carData_3.0-5       farver_2.1.0        ggsignif_0.6.3
[53] reshape2_1.4.4      ragg_1.2.1          ellipsis_0.3.2      generics_0.1.1
[57] vctrs_0.3.8         cowplot_1.1.1       boot_1.3-28         sandwich_3.0-1
[61] lava_1.6.10         tools_4.1.1         glue_1.6.1          purrr_0.3.4
[65] abind_1.4-5         parallel_4.1.1      colorspace_2.0-2    rstatix_0.7.0
```

References

Oldford, R. W. (2016). Self-calibrating quantile–quantile plots. *The American Statistician*, 70(1):74–90.

Pipper, C. B., Ritz, C., and Bisgaard, H. (2012). A versatile method for confirmatory evaluation of the effects of a covariate in multiple models. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*, 61(2):315–326.

Appendix A Likelihood in a linear mixed model

Denote by $\boldsymbol{Y}$ a vector of m outcomes, $\boldsymbol{X}$ a vector of p covariates, $\mu(\boldsymbol{\Theta}, \boldsymbol{X})$ the modeled mean, and $\Omega(\boldsymbol{\Theta}, \boldsymbol{X})$ the modeled residual variance-covariance. We consider n replicates (i.e. $\boldsymbol{Y}_1, \dots, \boldsymbol{Y}_n$) and $VX_1, \dots, \boldsymbol{X}_n$) along with a vector of weights $\omega = (w_1, \dots, w_n)$, which are by default all equal to 1.

A.1 Log-likelihood

The restricted log-likelihood in a linear mixed model can then be written:

$$\begin{aligned}\mathcal{L}(\boldsymbol{\Theta}|\boldsymbol{Y}, \boldsymbol{X}) =& \frac{p}{2}\log(2\pi) - \frac{1}{2}\log\left(\left|\sum_{i=1}^{n} w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta})\boldsymbol{X}_i^\intercal\right|\right) \\ &+ \sum_{i=1}^{n} w_i \left(-\frac{m}{2}\log(2\pi) - \frac{1}{2}\log|\Omega_i(\boldsymbol{\Theta})| - \frac{1}{2}(\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta}, \boldsymbol{X}_i))\Omega_i(\boldsymbol{\Theta})^{-1}(\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta}, \boldsymbol{X}_i))^\intercal\right)\end{aligned} \tag{A}$$

This is what the `logLik` method is computing for the REML criteria. The red term is specific to the REML criteria and prevents from computing individual contributions to the likelihood[4]. The blue term is what `logLik` outputs for the ML criteria when setting the argument `indiv` to `TRUE`.

A.2 Score

Using that $\partial \log(\det(X)) = tr(X^{-1}\partial(X))$, the score is obtained by derivating once the log-likelihood, i.e., for $\theta \in \boldsymbol{\Theta}$:

$$\begin{aligned}\mathcal{S}(\theta) =& \frac{\partial \mathcal{L}(\boldsymbol{\Theta}|\boldsymbol{Y}, \boldsymbol{X})}{\partial \theta} = \frac{1}{2} tr\left(\left(\sum_{i=1}^{n} w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta})\boldsymbol{X}_i^\intercal\right)^{-1}\left(\sum_{i=1}^{n} w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta})\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial \theta}\Omega_i(\boldsymbol{\Theta})^{-1}\boldsymbol{X}_i^\intercal\right)\right) \\ &+ \sum_{i=1}^{n} w_i \left(-\frac{1}{2} tr\left(\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial \theta}\right) + \frac{\partial \mu(\boldsymbol{\Theta}, \boldsymbol{X}_i)}{\partial \theta}\Omega_i(\boldsymbol{\Theta})^{-1}(\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta}, \boldsymbol{X}_i))^\intercal \right. \\ &\left. + \frac{1}{2}(\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta}, \boldsymbol{X}_i))\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial \theta}\Omega_i(\boldsymbol{\Theta})^{-1}(\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta}, \boldsymbol{X}_i))^\intercal\right).\end{aligned}$$

This is what the `score` method is computing for the REML criteria. The red term is specific to the REML criteria and prevents from computing the score relative to each cluster. The blue term is what `score` outputs for the ML criteria when setting the argument `indiv` to `TRUE`.

[4]The REML is the likelihood of the observations divided by the prior on the estimated mean parameters $\widehat{\boldsymbol{\Theta}}_\mu \sim \mathcal{N}(\mu, \left(\boldsymbol{X}\Omega^{-1}(\boldsymbol{\Theta})\boldsymbol{X}^\intercal\right)^{-1})$. This corresponds to $\frac{1}{\sqrt{2\pi}^p\left|\left(\sum_{i=1}^{n}\boldsymbol{X}_i\Omega_i^{-1}(\boldsymbol{\Theta})\boldsymbol{X}_i^\intercal\right)^{-1}\right|}\exp\left(-(\widehat{\boldsymbol{\Theta}}_\mu - \mu)\left(2\sum_{i=1}^{n}\boldsymbol{X}_i\Omega_i^{-1}(\boldsymbol{\Theta})\boldsymbol{X}_i^\intercal\right)^{-1})(\widehat{\boldsymbol{\Theta}}_\mu - \mu)^\intercal\right)$ Since μ will be estimated to be $\boldsymbol{\Theta}_\mu$, the exponential term equals 1 and thus does not contribute to the log-likelihood. One divided by the other term gives $\sqrt{2\pi}^p\left(\left|\sum_{i=1}^{n}\boldsymbol{X}_i\Omega_i^{-1}(\boldsymbol{\Theta})\boldsymbol{X}_i^\intercal\right|\right)^{-1}$. The log of this term equals the red term

A.3 Hessian

Derivating a second time the log-likelihood gives the hessian, $\mathcal{H}(\boldsymbol{\Theta})$, with element[5]:

$$
\begin{aligned}
&\mathcal{H}(\theta,\theta') = \frac{\partial^2 \mathcal{L}(\boldsymbol{\Theta}|\boldsymbol{Y},\boldsymbol{X})}{\partial\theta\partial\theta'} = \frac{\partial \mathcal{S}(\theta)}{\partial\theta'} \\
=&\frac{1}{2} tr\left(\left(\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta}) \boldsymbol{X}_i^\intercal\right)^{-1} \left\{\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta}) \left(\frac{\partial^2 \Omega_i(\boldsymbol{\Theta})}{\partial\theta\partial\theta'} - 2\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta}\Omega_i^{-1}(\boldsymbol{\Theta})\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta'}\right)\Omega_i(\boldsymbol{\Theta})^{-1}\boldsymbol{X}_i^\intercal \right.\right. \\
&\left.\left. + \left(\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta})\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta}\Omega_i(\boldsymbol{\Theta})^{-1}\boldsymbol{X}_i^\intercal\right)\left(\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta}) \boldsymbol{X}_i^\intercal\right)^{-1}\left(\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta})\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta'}\Omega_i(\boldsymbol{\Theta})^{-1}\boldsymbol{X}_i^\intercal\right)\right\}\right) \\
&+ \sum_{i=1}^n w_i \left(\frac{1}{2} tr\left(\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta'}\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta} - \Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial^2 \Omega_i(\boldsymbol{\Theta})}{\partial\theta\partial\theta'}\right)\right. \\
&\quad - \frac{\partial \mu(\boldsymbol{\Theta},\boldsymbol{X}_i)}{\partial\theta}\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta'}\Omega_i(\boldsymbol{\Theta})^{-1}\boldsymbol{\varepsilon}_i(\boldsymbol{\Theta})^\intercal - \frac{\partial \mu(\boldsymbol{\Theta},\boldsymbol{X}_i)}{\partial\theta}\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \mu(\boldsymbol{\Theta},\boldsymbol{X}_i)^\intercal}{\partial\theta'} \\
&\quad \left. + \frac{1}{2}\boldsymbol{\varepsilon}_i(\boldsymbol{\Theta})\Omega_i(\boldsymbol{\Theta})^{-1}\left(\frac{\partial^2 \Omega_i(\boldsymbol{\Theta})}{\partial\theta\partial\theta'} - \frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta'}\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta} - \frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta}\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta'}\right)\Omega_i(\boldsymbol{\Theta})^{-1}\boldsymbol{\varepsilon}_i(\boldsymbol{\Theta})^\intercal\right).
\end{aligned}
$$

where $\boldsymbol{\varepsilon}_i(\boldsymbol{\Theta}) = \boldsymbol{Y}_i - \mu(\boldsymbol{\Theta},\boldsymbol{X}_i)$.

The `information` method will (by default) return the (observed) information which is the opposite of the hessian. So multiplying the previous formula by -1 gives what `information` output for the REML criteria. The red term is specific to the REML criteria and prevents from computing the information relative to each cluster. The blue term is what `information` outputs for the ML criteria (up to a factor -1) when setting the argument `indiv` to `TRUE`.

A possible simplification is to use the expected hessian at the maximum likelihood. Indeed for any deterministic matrix A:

- $\mathbb{E}\left[A(\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta},\boldsymbol{X}_i))^\intercal|\boldsymbol{X}_i\right] = 0$
- $\mathbb{E}\left[(\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta},\boldsymbol{X}_i))A(\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta},\boldsymbol{X}_i))^\intercal||\boldsymbol{X}_i\right] = tr(A\mathbb{V}ar(\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta},\boldsymbol{X}_i)))$

when $\mathbb{E}\left[\boldsymbol{Y}_i - \mu(\boldsymbol{\Theta},\boldsymbol{X}_i)\right] = 0$. This leads to:

$$
\begin{aligned}
&\mathbb{E}\left[\mathcal{H}(\theta,\theta')|\boldsymbol{X}\right] \\
&= \frac{1}{2} tr\left(\left(\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta}) \boldsymbol{X}_i^\intercal\right)^{-1} \left\{\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta}) \left(\frac{\partial^2 \Omega_i(\boldsymbol{\Theta})}{\partial\theta\partial\theta'} - 2\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta}\Omega_i^{-1}(\boldsymbol{\Theta})\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta'}\right)\Omega_i(\boldsymbol{\Theta})^{-1}\boldsymbol{X}_i^\intercal \right.\right. \\
&\left.\left. + \left(\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta})\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta}\Omega_i(\boldsymbol{\Theta})^{-1}\boldsymbol{X}_i^\intercal\right)\left(\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta}) \boldsymbol{X}_i^\intercal\right)^{-1}\left(\sum_{i=1}^n w_i \boldsymbol{X}_i \Omega_i^{-1}(\boldsymbol{\Theta})\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta'}\Omega_i(\boldsymbol{\Theta})^{-1}\boldsymbol{X}_i^\intercal\right)\right\}\right) \\
&+ \sum_{i=1}^n w_i \left(-\frac{1}{2} tr\left(\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta'}\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial\theta}\right) - \frac{\partial \mu(\boldsymbol{\Theta},\boldsymbol{X}_i)}{\partial\theta}\Omega_i(\boldsymbol{\Theta})^{-1}\frac{\partial \mu(\boldsymbol{\Theta},\boldsymbol{X}_i)^\intercal}{\partial\theta'}\right) \qquad \text{(B)}
\end{aligned}
$$

This is what `information` output when the argument `type.information` is set to `"expected"` (up to a factor -1).

[5] if one is relative to the mean and the other to the variance then they are respectively θ and θ'

A.4 Degrees of freedom

Degrees of freedom are computed using a Satterthwaite approximation, i.e. for an estimate coefficient $\widehat{\beta} \in \widehat{\boldsymbol{\Theta}}$ with standard error $\sigma_{\widehat{beta}}$, the degree of freedom is:

$$df\left(\sigma_{\widehat{\beta}}\right) = \frac{2\sigma_{\widehat{\beta}}^4}{\mathbb{V}ar\left[\widehat{\sigma}_{\widehat{\beta}}\right]}$$

Using a first order Taylor expansion we can approximate the variance term as:

$$\begin{aligned}\mathbb{V}ar\left[\widehat{\sigma}_{\widehat{\beta}}\right] &\approx \frac{\partial \widehat{\sigma}_{\widehat{\beta}}}{\partial \boldsymbol{\Theta}} \Sigma_{\boldsymbol{\Theta}} \frac{\partial \widehat{\sigma}_{\widehat{\beta}}}{\partial \boldsymbol{\Theta}}^\intercal \\ &\approx c_\beta \left(\widehat{\mathcal{I}}_{\widehat{\boldsymbol{\Theta}}}\right)^{-1} \frac{\partial \widehat{\mathcal{I}}_{\widehat{\boldsymbol{\Theta}}}}{\partial \boldsymbol{\Theta}} \left(\widehat{\mathcal{I}}_{\widehat{\boldsymbol{\Theta}}}\right)^{-1} c_\beta{}^\intercal \Sigma_{\boldsymbol{\Theta}} c_\beta{}^\intercal \left(\widehat{\mathcal{I}}_{\widehat{\boldsymbol{\Theta}}}\right)^{-1} \frac{\partial \widehat{\mathcal{I}}_{\widehat{\boldsymbol{\Theta}}}}{\partial \boldsymbol{\Theta}}^\intercal \left(\widehat{\mathcal{I}}_{\widehat{\boldsymbol{\Theta}}}\right)^{-1} c_\beta\end{aligned}$$

where $\Sigma_{\boldsymbol{\Theta}}$ is the variance-covariance matrix of all model coefficients, $\mathcal{I}_{\boldsymbol{\Theta}}$ the information matrix for all model coefficients, c_β a matrix used to select the element relative to β in the first derivative of the information matrix, and $\frac{\partial .}{\partial \boldsymbol{\Theta}}$ denotes the vector of derivatives with respect to all model coefficients.

The derivative of the information matrix (i.e. negative hessian) can then be computed using numerical derivatives or using analytical formula. To simplify the derivation of the formula we will only derive them at the maximum likelihood, i.e. when $\mathbb{E}\left[\frac{\partial \mathcal{H}(\theta,\theta'|\boldsymbol{X})}{\partial \theta''}\right] = \frac{\partial \mathbb{E}[\mathcal{H}(\theta,\theta'|\boldsymbol{X})]}{\partial \theta''}$ where the expectation is taken over $\boldsymbol{X}$. We can therefore take the derivative of formula (B). We first note that its derivative with respect to the mean parameters is 0. So we just need to compute the derivative with respect to a variance parameter θ'':

$$\begin{aligned}&\frac{\partial \mathbb{E}\left[\mathcal{H}(\theta,\theta')|\boldsymbol{X}\right]}{\partial \theta''} \\ &+ \sum_{i=1}^{n} w_i \left(-\frac{1}{2} tr\left(-2\Omega_i(\boldsymbol{\Theta})^{-1} \frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial \theta''} \Omega_i(\boldsymbol{\Theta})^{-1} \frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial \theta'} \Omega_i(\boldsymbol{\Theta})^{-1} \frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial \theta} \right.\right. \\ &\qquad \left. + \Omega_i(\boldsymbol{\Theta})^{-1} \frac{\partial^2 \Omega_i(\boldsymbol{\Theta})}{\partial \theta' \partial \theta''} \Omega_i(\boldsymbol{\Theta})^{-1} \frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial \theta} + \Omega_i(\boldsymbol{\Theta})^{-1} \frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial \theta'} \Omega_i(\boldsymbol{\Theta})^{-1} \frac{\partial^2 \Omega_i(\boldsymbol{\Theta})}{\partial \theta \partial \theta''} \right) \\ &\qquad \left. + \frac{\partial \mu(\boldsymbol{\Theta}, \boldsymbol{X}_i)}{\partial \theta} \Omega_i(\boldsymbol{\Theta})^{-1} \frac{\partial \Omega_i(\boldsymbol{\Theta})}{\partial \theta''} \Omega_i(\boldsymbol{\Theta})^{-1} \frac{\partial \mu(\boldsymbol{\Theta}, \boldsymbol{X}_i)}{\partial \theta'}^\intercal \right)\end{aligned}$$

Appendix B Likelihood ratio test with the REML criterion

The blue term of Equation A in the log-likelihood is invariant to re-parameterisation while the red term is not. This means that a re-parametrisation of X into $\tilde{X} = BX$ with B invertible would not change the likelihood when using ML but would decrease the log-likelihood by $\log(|B|)$ when using REML.

```
LMMstar.options(optimizer = "FS",
  param.optimizer = c(n.iter = 1000, tol.score = 1e-3, tol.param = 1e-5))
```

Let's take an example:

```
## data(gastricbypassL, package = "LMMstar")
dfTest <- gastricbypassL
dfTest$glucagon2 <- dfTest$glucagon*2
```

where we multiply one column of the design matrix by 2. As mentionned previously this does not affect the log-likelihood when using ML:

```
logLik(lmm(weight ~ glucagon, data = dfTest, structure = UN(~time|id), method = "ML"))
logLik(lmm(weight ~ glucagon2, data = dfTest, structure = UN(~time|id), method = "ML"))
```

```
[1] -245.7909
[1] -245.7909
```

but it does when using REML:

```
logLik(lmm(weight ~ glucagon, data = dfTest, structure = UN(~time|id), method = "REML"))
logLik(lmm(weight ~ glucagon2, data = dfTest, structure = UN(~time|id), method = "REML"))
log(2)
```

```
[1] -245.0382
[1] -245.7313
[1] 0.6931472
```

Therefore, when comparing models with different mean effects there is a risk that the difference (or part of it) in log-likelihood is due to a new parametrisation and no only to a difference in model fit. This would typically be the case when adding an interaction where we can have a smaller restricted log-likehood when considering a more complex model:

```
set.seed(1)
dfTest$ff <- rbinom(NROW(dfTest), size = 1, prob = 0.5)
logLik(lmm(weight ~ glucagon, data = dfTest, structure = UN(~time|id), method = "REML"))
logLik(lmm(weight ~ glucagon*ff, data = dfTest, structure = UN(~time|id), method = "REML"))
```

```
[1] -245.0382
[1] -245.3555
```

This is quite counter-intuitive as more complex model should lead to better fit and would never happen when using ML:

```
logLik(lmm(weight ~ glucagon, data = dfTest, structure = UN(~time|id), method = "ML"))
logLik(lmm(weight ~ glucagon*ff, data = dfTest, structure = UN(~time|id), method = "ML"))
```

```
[1] -245.7909
[1] -245.3593
```

This is why, unless one knows what he/she is doing, it is not recommanded to use likelihood ratio test to assess relevance of mean parameters in mixed models estimated with REML.