

# Overview of the package LMMstar

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June 17, 2021

This vignette describes the main functionalities of the **LMMstar** package. This package implements specific types of multivariate Gaussian models mainly useful when having repeated observations over a discrete variable (e.g. time, brain region, ...). Key assumptions are that at the cluster level, observations are independent and identically distributed and that the mean and variance are driven by independent factors. 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 multivariate Gaussian models. The user can interact with *lmm* objects using:
  - `anova` to test combinations of coefficients (Wald test or Likelihood ratio tests)
  - `coef` to extract the estimates.
  - `confint` to extract estimates, confidence intervals, and p.values.
  - `getVarCov` to extract the modeled residual variance covariance matrix.
  - `logLik` to output the log-likelihood of the estimated model.
  - `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 results
- 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. function. 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 **veteran** dataset:

```
data(gastricbypassL)
head(gastricbypassL)
```

```
   id visit                time weight glucagon
1   1     1 3 months before surgery 127.2  5032.50
2   2     1 3 months before surgery 165.2 12142.50
3   3     1 3 months before surgery 109.7 10321.35
4   4     1 3 months before surgery 146.2  6693.00
5   5     1 3 months before surgery 113.1  7090.50
6   6     1 3 months before surgery 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 surgery", "1 week before surgery",
    "1 week after surgery", "3 months after surgery" ),
  labels = c("B3_months", "B1_week", "A1_week", "A3_months"))
```

and rescale the glucagon values

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

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 is:

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

```
[1] '0.2.1'
```

# 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	128.9700	20.269	100.900	123.1000	173.000
2	weight	B1_week	20	0	121.2400	18.910	95.700	114.5000	162.200
3	weight	A1_week	20	0	115.7000	18.275	89.900	110.6000	155.000
4	weight	A3_months	20	0	102.3650	17.054	78.800	98.5000	148.000
5	glucagon	B3_months	20	0	-0.4856	0.641	-1.395	-0.6679	1.030
6	glucagon	B1_week	19	1	-0.6064	0.558	-1.416	-0.7669	0.946
7	glucagon	A1_week	19	1	1.0569	1.044	-0.478	0.9408	3.267
8	glucagon	A3_months	20	0	0.0576	0.760	-1.047	0.0319	2.124

## 2 Multivariate Gaussian model

### 2.1 Modeling tools

Fit a multivariate Gaussian model with **compound symmetry** structure:

```
eCS.lmm <- lmm(weight ~ time + glucagon,
               structure = CS(~time|id),
               data = gastricbypassL)
eCS.lmm
```

Multivariate Gaussian Model with a compound symmetry covariance matrix

```
data          : 78 observations and distributed in 20 clusters
log-likelihood : -243.6005
parameters    : 5 mean ((Intercept) timeB1_week timeA1_week timeA3_months glucagon)
                1 variance (sigma)
                1 correlation (Rho)
```

Fit a multivariate Gaussian model with **unstructured** covariance matrix:

```
eUN.lmm <- lmm(weight ~ time + glucagon,
               structure = UN(~time|id),
               data = gastricbypassL)
eUN.lmm
```

Multivariate Gaussian Model with an unstructured covariance matrix

```
data          : 78 observations and distributed in 20 clusters
log-likelihood : -216.3189
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 (cor(B1_week,B3_months) cor(A1_week,B3_months) cor(A3_months,B3_months))
```

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 reasonable computation time.

## 2.2 Model output

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

```
summary(eCS.lmm, ci = TRUE)
```

```
Multivariate Gaussian Model with a compound symmetry covariance matrix
- fitted using Restricted Maximum Likelihood (REML)
- log-likelihood :-243.6005 (parameters: mean = 5, variance = 1, correlation = 1)
```

Dataset: `gastricbypassL`

- 20 clusters
- 78 observations were analyzed, 2 were excluded because of missing values
- 4 maximum number of observations per cluster
- levels of the categorical variables
- reference level: `time=B3_months`

\$time

	B1_week	A1_week	A3_months
B3_months	0	0	0
B1_week	1	0	0
A1_week	0	1	0
A3_months	0	0	1

Correlation structure: `~1 | id`

	B3_months	B1_week	A1_week	A3_months
B3_months	1.00	0.97	0.97	0.97
B1_week	0.97	1.00	0.97	0.97
A1_week	0.97	0.97	1.00	0.97
A3_months	0.97	0.97	0.97	1.00

Variance structure: `~1`

	standard.deviation
sigma	18.84957

Mean structure: `weight ~ time + glucagon`

	estimate	se	df	lower	upper	p.value	
(Intercept)	129.369	4.226	20.034	120.556	120.556	<0.001	***
timeB1_week	-7.619	1.054	53.968	-9.732	-9.732	<0.001	***
timeA1_week	-14.495	1.428	53.879	-17.358	-17.358	<0.001	***
timeA3_months	-27.051	1.087	53.943	-29.231	-29.231	<0.001	***
glucagon	0.822	0.62	53.81	-0.421	-0.421	0.191	

The columns lower and upper correspond to the 95% confidence interval of the estimated coefficient  
Note: p-values and confidence intervals are not adjusted for multiple comparisons

## 2.3 Extract estimated coefficients

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

```
coef(eCS.lmm)
```

(Intercept)	timeB1_week	timeA1_week	timeA3_months	glucagon	log(sigma)	atanh(Rho)
129.3690995	-7.6194918	-14.4951323	-27.0514694	0.8217879	2.9364900	2.0911816

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
20.28080	19.04553	17.65479	16.76104

## 2.4 Extract estimated residual variance-covariance structure

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

```
nlme::getVarCov(eCS.lmm)
```

	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

It can also be specific to an individual:

```
nlme::getVarCov(eCS.lmm, individual = 5)
```

	B3_months	A1_week	A3_months
B3_months	355.3062	344.6236	344.6236
A1_week	344.6236	355.3062	344.6236
A3_months	344.6236	344.6236	355.3062

## 2.5 Model diagnostic

The method `residuals` can be used to output the normalized residuals in a wide format:

```
eCS.diag <- residuals(eCS.lmm, type.residual = "normalized", format = "wide")
```

This can for instance be used to check the auto-correlation between the residuals:

```
cor(eCS.diag[,-1,drop=FALSE], use = "pairwise")
```

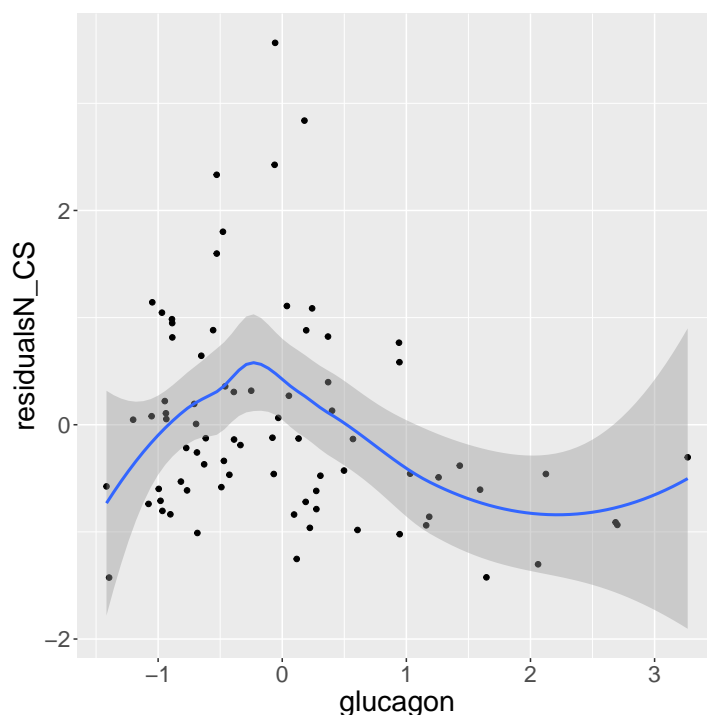
```
      B3_months  B1_week  A1_week A3_months  
B3_months 1.0000000 0.6819780 0.5924644 0.3844298  
B1_week   0.6819780 1.0000000 0.7996891 0.2103374  
A1_week   0.5924644 0.7996891 1.0000000 0.2533221  
A3_months 0.3844298 0.2103374 0.2533221 1.0000000
```

The long format:

```
gastricbypassL$residualsN_CS <- residuals(eCS.lmm, type.residual = "normalized",  
  format = "long")
```

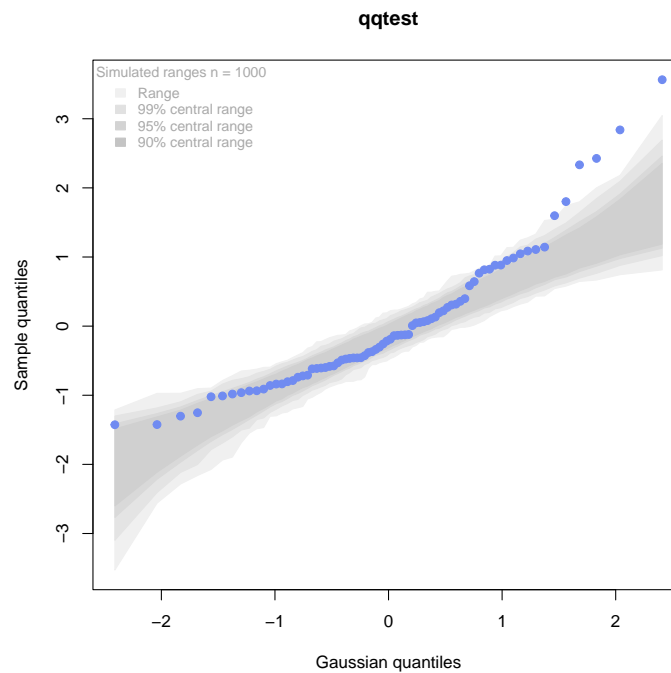
can be useful to investigate trends relative to a covariate:

```
library(ggplot2)  
ggplot(gastricbypassL, aes(x=glucagon,y=residualsN_CS)) + geom_point() + geom_smooth()
```



or to look at the distribution of the residuals via a qq-plot:

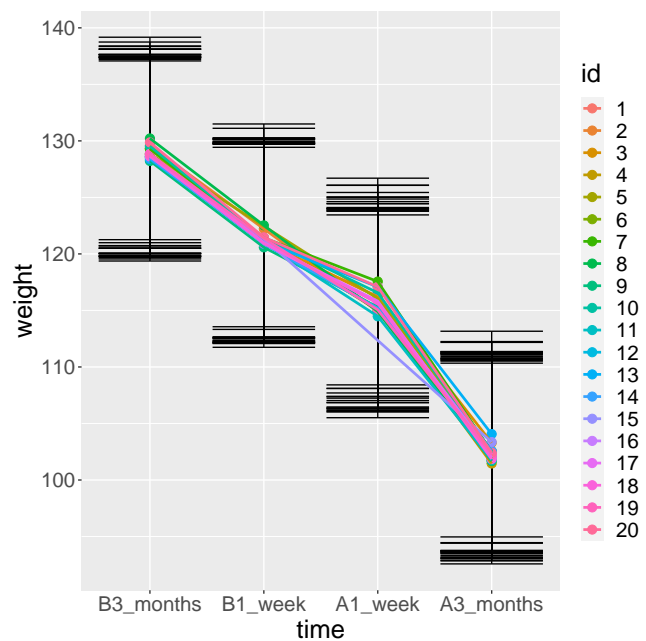
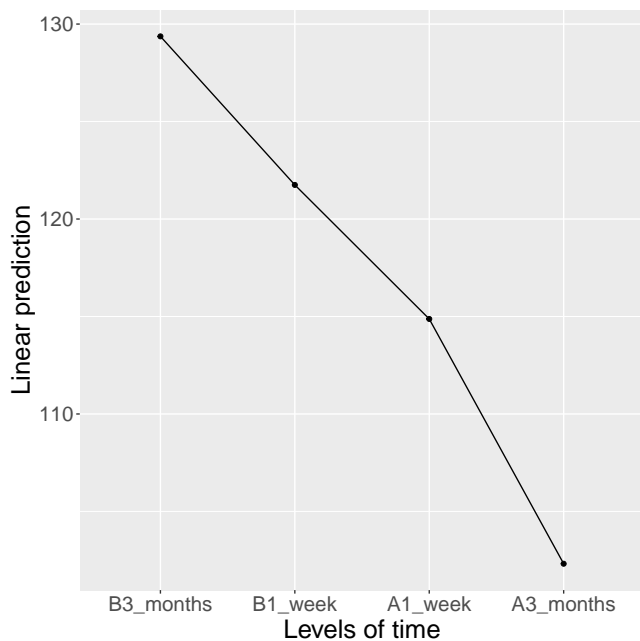
```
library(qqtest)
qqtest(na.omit(gastricbypassL$residualsN_CS))
```



## 2.6 Model fit

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

```
library(emmeans) ## left panel
emmip(eCS.lmm, ~time)
library(ggplot2) ## right panel
autoplot(eCS.lmm)
```





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

```
autoplot(eCS.lmm, at = data.frame(glucagon = 10), color = "glucagon")
```

## 2.7 Statistical inference

### 2.7.1 Model coefficients

The estimated coefficients with their confidence intervals can be accessed via the `confint` method:

```
confint(eCS.lmm)
```

	estimate	se	statistic	df	lower	upper	null	p.value
(Intercept)	129.3690995	4.2256318	30.615327	20.03432	120.5555539	138.182645	0	0.000000e+00
timeB1_week	-7.6194918	1.0538287	-7.230294	53.96824	-9.7323197	-5.506664	0	1.746652e-09
timeA1_week	-14.4951323	1.4279524	-10.150991	53.87927	-17.3581515	-11.632113	0	4.130030e-14
timeA3_months	-27.0514694	1.0870651	-24.884866	53.94292	-29.2309565	-24.871982	0	0.000000e+00
glucagon	0.8217879	0.6199685	1.325532	53.80984	-0.4212748	2.064851	0	1.905952e-01
log(sigma)	2.9364900	0.1587900	NA	16.79510	2.6011608	3.271819	NA	NA
atanh(Rho)	2.0911816	0.1874830	11.153979	29.43362	1.7079810	2.474382	0	4.330536e-12

The variance and correlation parameters being constrained parameters (e.g. strictly positive), they uncertainty is by default computed after transformation (e.g. `log`):

```
confint(eCS.lmm, effects = "variance")
```

	estimate	se	statistic	df	lower	upper	null	p.value
log(sigma)	2.93649	0.15879	NA	16.7951	2.601161	3.271819	NA	NA

They can be backtransformed to the original scale using `backtransform`:

```
backtransform(confint(eCS.lmm, effects = "variance"))
```

	estimate	se	statistic	df	lower	upper	null	p.value
sigma	18.84957	0.15879	NA	16.7951	13.47938	26.35925	NA	NA

Note: estimates and confidence intervals for sigma, k, rho have been back-transformed.  
standard errors are not back-transformed.

While not recommended, it is also possible to not use any transformation:

```
table <- confint(eCS.lmm, effects = "variance", transform.sigma = "none")
table
```

	estimate	se	statistic	df	lower	upper	null	p.value
sigma	18.84957	2.993123	NA	2.695584	8.685673	29.01346	NA	NA

## 2.7.2 Linear combination of the model coefficients

The `anova` method can be used to test one or several linear combinations of the model coefficients using Wald tests. For instance whether there is a change in average weight just after taking the treatment:

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

```

                ** User-specified hypotheses **

- F-test
statistic df.num df.denom      p.value
  43.14145      1 17.87461 3.723244e-06

- P-values and confidence interval (adjusted for multiplicity within each global test)
              estimate      se      df statistic      lower      upper null
timeA1_week - timeB1_week -3.905721 0.5946396 17.87461 -6.568215 -5.155641 -2.655801      0
              p.value
timeA1_week - timeB1_week 3.723244e-06
```

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, rhs = rhs, df = df, ci = ci, :
```

```
Possible misspecification of the argument 'effects' as running mulcomp::glht lead to the following
```

```
Error in parse(text = ex[i]) : <text>:1:7: unexpected symbol
```

```
1: log(k).B1_week
```

```
^
```

It is then advised to specify the null hypothesis via a contrast matrix, e.g.:

```
name.coef <- names(coef(eUN.lmm))
name.varcoef <- grep("log(k)", name.coef, value = TRUE, fixed = TRUE)
C <- matrix(0, nrow = 3, ncol = length(name.coef), dimnames = list(name.varcoef, name.coef))
diag(C[name.varcoef, name.varcoef]) <- 1

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

```

                ** User-specified hypotheses **

- F-test
statistic df.num df.denom      p.value
  6.203176      3 17.99457 0.004417066
```

## 2.8 Baseline adjustment

The `lmm` contains an "experimental" feature to drop non-identifiable effects from the model. For instance, let us define two (artificial) 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$treatment <- factor(gastricbypassL$group, c("none","1","2"))
gastricbypassL$treatment[gastricbypassL$time %in% c("B3_months","B1_week")] <- "none"
table(gastricbypassL$treatment, gastricbypassL$time)
```

	B3_months	B1_week	A1_week	A3_months
none	20	20	0	0
1	0	0	14	14
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 ~ treatment*time, data = gastricbypassL))
```

```
[1] "(Intercept)"          "treatment1"          "treatment2"
[4] "timeB1_week"          "timeA1_week"         "timeA3_months"
[7] "treatment1:timeB1_week" "treatment2:timeB1_week" "treatment1:timeA1_week"
[10] "treatment2:timeA1_week" "treatment1:timeA3_months" "treatment2: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 ~ treatment*time, data = gastricbypassL, structure = UN(~time|id))
```

Warning message:

In `model.matrix_regularize(formula.mean, data)` :

Constant values in the design matrix in interactions "treatment:time"

Coefficients "treatment1" "treatment2" "timeA1\_week" "timeA3\_months" "treatment1:timeB1\_week" "tre

Consider defining manually the interaction, e.g. via `droplevels(interaction(.,.))` to avoid this war

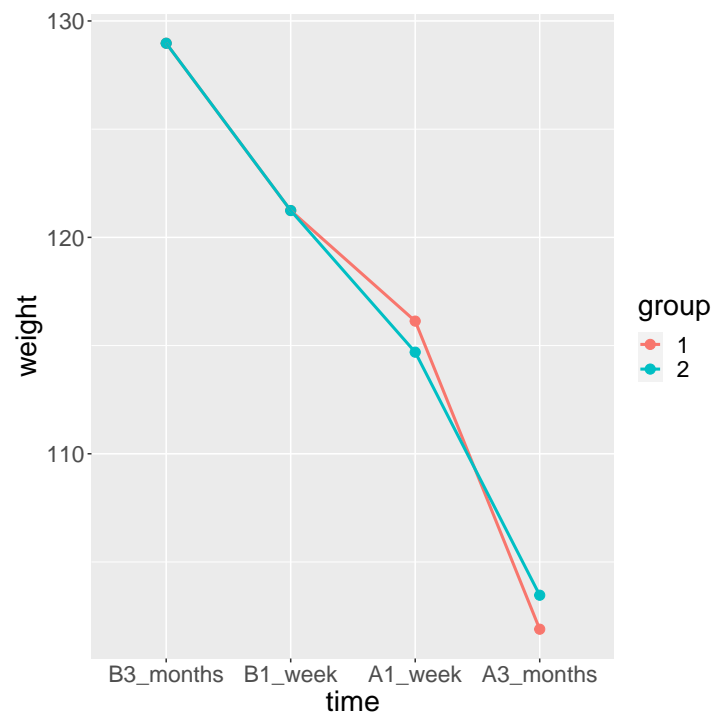
with the following coefficients:

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

	(Intercept)	timeB1_week	treatment1:timeA1_week	treatment2:timeA1_week
	128.97000	-7.73000	-12.83949	-14.27452
treatment1:timeA3_months				
treatment2:timeA3_months				
	-27.07620	-25.50553		

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

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



### 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 4.1.0 (2021-05-18)

Platform: x86\_64-pc-linux-gnu (64-bit)

Running under: Ubuntu 20.04.2 LTS

Matrix products: default

BLAS: /usr/lib/x86\_64-linux-gnu/blas/libblas.so.3.9.0

LAPACK: /usr/lib/x86\_64-linux-gnu/lapack/liblapack.so.3.9.0

locale:

```
[1] LC_CTYPE=en_US.UTF-8      LC_NUMERIC=C               LC_TIME=en_US.UTF-8
[4] LC_COLLATE=en_US.UTF-8    LC_MONETARY=en_US.UTF-8    LC_MESSAGES=en_US.UTF-8
[7] LC_PAPER=en_US.UTF-8      LC_NAME=C                   LC_ADDRESS=C
[10] LC_TELEPHONE=C            LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
```

attached base packages:

```
[1] stats      graphics  grDevices  utils      datasets  methods    base
```

other attached packages:

```
[1] LMMstar_0.2
```

loaded via a namespace (and not attached):

```
[1] Rcpp_1.0.6      plyr_1.8.6      pillar_1.6.1    compiler_4.1.0
[5] tools_4.1.0     lifecycle_1.0.0 tibble_3.1.2    gtable_0.3.0
[9] nlme_3.1-152    lattice_0.20-44 pkgconfig_2.0.3 rlang_0.4.11
[13] Matrix_1.3-3    mvtnorm_1.1-1    coda_0.19-4     stringr_1.4.0
[17] dplyr_1.0.6     generics_0.1.0   vctrs_0.3.8     grid_4.1.0
[21] tidyselect_1.1.1 glue_1.4.2       R6_2.5.0        fansi_0.4.2
[25] survival_3.2-11 multcomp_1.4-17  lava_1.6.9      TH.data_1.0-10
[29] reshape2_1.4.4  ggplot2_3.3.3    purrr_0.3.4     magrittr_2.0.1
[33] scales_1.1.1    codetools_0.2-18 ellipsis_0.3.2   emmeans_1.6.0
[37] MASS_7.3-54     splines_4.1.0    xtable_1.8-4     colorspace_2.0-1
[41] numDeriv_2016.8-1.1 sandwich_3.0-1    utf8_1.2.1      stringi_1.6.2
[45] estimability_1.3 munsell_0.5.0    crayon_1.4.1     zoo_1.8-9
```

## References



# Appendix A Likelihood in a multivariate Gaussian models

## A.1 Log-likelihood

Denote by  $\mathbf{Y}$  a vector of  $m$  outcomes,  $\mathbf{X}$  a vector of  $p$  covariates,  $\mu(\boldsymbol{\Theta}, \mathbf{X})$  the modeled mean, and  $\Omega(\boldsymbol{\Theta}, \mathbf{X})$  the modeled residual variance-covariance. The restricted log-likelihood in a linear Gaussian model can then be written:

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

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<sup>1</sup>. The blue term is what `logLik` outputs for the ML criteria when setting the argument `indiv` to `TRUE`.

## A.2 Score

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

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

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`.

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<sup>1</sup>The REML is the likelihood of the observations divided by the prior on the estimated mean parameters  $\hat{\boldsymbol{\Theta}}_\mu \sim \mathcal{N}(\mu, (\mathbf{X} \Omega^{-1}(\boldsymbol{\Theta}) \mathbf{X}^\top)^{-1})$ . This corresponds to  $\frac{1}{\sqrt{2\pi^p} |(\sum_{i=1}^n \mathbf{X}_i \Omega_i^{-1}(\boldsymbol{\Theta}) \mathbf{X}_i^\top)^{-1}|} \exp \left( -(\hat{\boldsymbol{\Theta}}_\mu - \mu) (2 \sum_{i=1}^n \mathbf{X}_i \Omega_i^{-1}(\boldsymbol{\Theta}) \mathbf{X}_i^\top)^{-1} (\hat{\boldsymbol{\Theta}}_\mu - \mu)^\top \right)$ . Since  $\mu$  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  $\sqrt{2\pi^p} |(\sum_{i=1}^n \mathbf{X}_i \Omega_i^{-1}(\boldsymbol{\Theta}) \mathbf{X}_i^\top)|^{-1}$ . The log of this term equals the red term

### A.3 Hessian

Derivating a second time the log-likelihood gives the hessian,  $\mathcal{H}(\Theta)$ , with element<sup>2</sup>:

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

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

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. Indeed for any deterministic matrix  $A$ :

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

Leading to:

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

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

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<sup>2</sup>if one is relative to the mean and the other to the variance then they are respectively  $\theta$  and  $\theta'$