Implementing Mixed Models with Repeated Measures (MMRM) in R

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Acknowledgements

Thanks to many in Product Development Data Sciences at Roche

Statistical Programmers
Francois Collin
Jennifer Li
Nick Paszty
Jana Stoilova

Core Developers
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Transformation to an R based workflow is ongoing

2019 2020 2021 2022

Regulatory SAS platform

Exploratory SAS platform

As the usage of SAS diminishes also the need for these platforms will fade out

Regulatory R platform

Validated transition solution

Illustration of overall R, Python, … usage

Illustration of overall SAS usage

DevOps Approach *Professional Statistical Software Engineering through Collaboration and Automation*

R-packages (NEST platform)

Other (e.g. Python, SAS, ..)

Mixed Models with Repeated Measures (MMRM)

Theory and Application in One Slide

Theory

MMRM = Special case of a Linear Mixed Model (LMM):

$\boldsymbol{Y}_i = \boldsymbol{X}_i\boldsymbol{\beta} + \boldsymbol{Z}_i\boldsymbol{b}_i + \boldsymbol{\varepsilon}_i$ for patient *i*, where

- $\boldsymbol{\beta}$ are the fixed effects, including visit-specific treatment effects
- $\boldsymbol{b}_i \sim N(\boldsymbol{0}, \boldsymbol{D})$ are the random effects, $\boldsymbol{\varepsilon}_i \sim N(\boldsymbol{0}, \boldsymbol{\Sigma})$ are the residuals
- Resulting marginal covariance matrix is $\boldsymbol{V}_i = \boldsymbol{Z}_i\boldsymbol{D}\boldsymbol{Z}_i^{\top} + \boldsymbol{\Sigma}$
- Marginal model is $\boldsymbol{Y}_i \sim N(\boldsymbol{X}_i\boldsymbol{\beta}, \boldsymbol{V}_i)$
- Restricted Maximum Likelihood Estimation of parameters

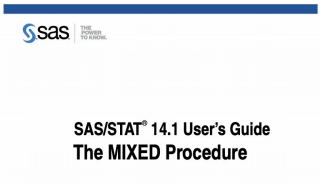
Application

Primary analysis of continuous endpoints in longitudinal clinical trials

- The time variable is categorical with a small number of “visits”
- Other covariates can be age, gender, baseline value of outcome, etc.
- Correlation between outcomes of the same patient is accounted for
- Typically want the marginal covariance matrix to be “unstructured”

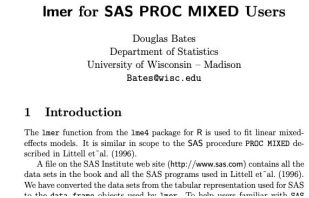
Challenge: How to implement MMRM in R to match SAS?

MMRM as one example where the transformation is non-trivial



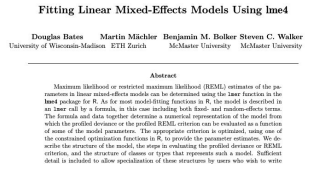
SAS: PROC MIXED as gold standard traditional proprietary software. Has many options for MMRM.

But: We want to move to R also for MMRM analysis.



R-package `nlme`: Classic mixed effects package with some transition guidance. Has options for covariance matrix specification.

But: Does not give Satterthwaite adjusted degrees of freedom and p-values.



R-packages `lme4` and `lmerTest`: Modern mixed effects packages that are actively being developed and give Satterthwaite adjustment.

But: Seemed like covariance matrix cannot be unstructured.

Step 1: Fit model with unstructured covariance with `lme4`

Problem

It seemed that `lme4` does not support unstructured covariance matrices.

Solution

- Look in detail whether this assumption is really true.
- Accept that we need to use random effects to model the covariance.
- However, if we nest the visit within the subject ID variable and disable some check, we can get it to work:

```
lmer(y ~ treatment + visit + (0 + visit | id), ...,
     control = lmerControl(check.nobs.vs.nRE = "ignore"))
```

(thanks to Brice Ozenne for his LMM vignette!)

- Not perfect, as we have one variance parameter too much here. But the covariance matrix as a whole is still identifiable. Just don't look at the "sigma" estimate separately.

Step 2: Multiple optimization algorithms improve convergence

Problem

Just using the default optimizer often failed convergence when fitting the LMM.

Solution

- First try default optimizer and see if it leads to convergence.
- If not, then try 6 additional optimizers:
  - If multiple of them work, then take the result which gives highest restricted likelihood.
  - If none of them work, only then fail.
- We can run these in parallel (multi-core) easily (at least on Unix):
  - Load percentage check can give us number of “free cores” on our RStudio server instance - so we can just say “`parallel = TRUE`”

Step 3: Calculate covariance estimate and model diagnostics

Problem

1. The default AIC, BIC, etc. in lme4 do not match SAS equivalents.
2. We need the marginal covariance matrix estimate for residual plots.

Solution

- Search mailing lists etc. to get starting point for covariance matrix calculations from fit internals
  - Take a patient with maximum number of visits
  - Helper function `lme4::getME()` allows access to fit internals
- Implement custom AIC, BIC, etc.
  - Needs effective number of variance parameters (from covariance)
- Lots of comparisons with SAS documentation and results
- Unit tests that make sure our results keep matching gold standard results

Results: Static production of MMRM tables and plots

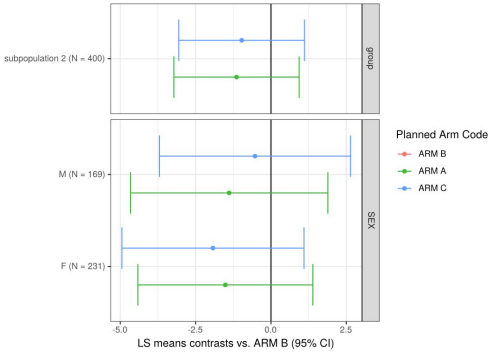
Leveraging our own rtables for tables and ggplot2 for plots

```
library(dplyr)
library(tern)
library(random.cdisc.data)

adsl <- radsl(cached = TRUE)
adqs <- radqs(cached = TRUE)
adqs_f <- adqs %>% ...

mmrm_results <- s_mmrm(
  vars = list(
    response = "AVAL",
    covariates = c("STRATA1", "BMRKR2"),
    id = "USUBJID",
    arm = "ARM",
    visit = "AVISIT"
  ),
  data = adqs_f,
  cor_struct = "unstructured",
  weights_emmeans = "proportional",
  optimizer = "automatic"
)
```

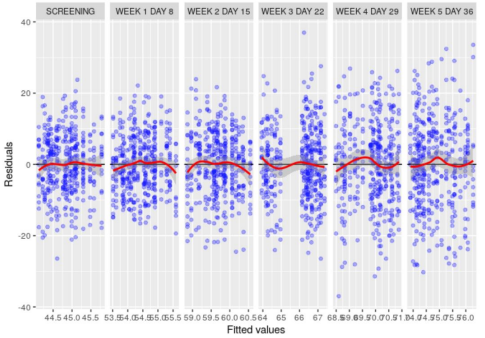
Code usage example

	B: Placebo (N=134)	A: Drug X (N=134)
	134	134
	45.190 (0.738)	44.578 (0.737)
	(43.739, 46.64)	(43.129, 46.028)
		-0.611 (1.044)
		(-2.664, 1.441)
		-1.4%
		0.5583
	134	134
	54.306 (0.689)	55.032 (0.688)
	(52.952, 55.661)	(53.679, 56.385)
		0.725 (0.975)
		(-1.191, 2.642)
		1.3%
		0.4572

Least square means table (only one part shown)



Forest plot for subgroups



Residuals vs. fitted values

~1900 LoC

700 for model fit etc.
900 for tables
300 for plots
(+similar for unit and regression tests)

4 Tables

1. Least square means
2. Fixed effect estimates
3. Covariance matrix
4. Model diagnostic stats

5 Plots

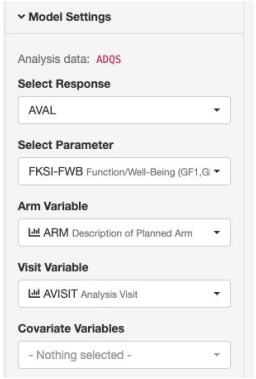
1. Least square means
2. Contrasts of LS means
3. Q-Q residuals
4. Residuals vs. fitted values
5. Forest plot for subgroups

2 Months

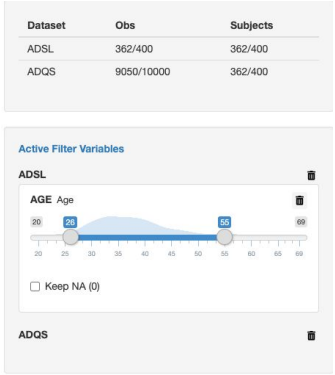
First discussions to release (part of our internal NEST R-package “tern” for statistical analyses)

Results: Interactive exploration via Shiny framework module

Via our teal framework - increases efficiency during study readout



Model specification



Filtering panel

Fit controls

Static R code production

Encodings

3 Encodings on left-hand side of the module:

1. Model specification
2. Output type
3. Output settings

Filtering

Standard data set filtering on right-hand side of the module.

Controls

- Parallel computing enabled (~50 cores RStudio server).
- Delayed reactivity via “Fit Model” button, as each fit takes at least 5 seconds.

Reproducible

“Show R Code” button produces the R code which can reproduce currently shown output in a static R session.

Outlook

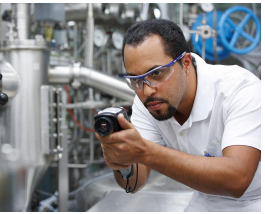
Next steps for leveraging the full value of our MMRM implementation

Validation: As part of next validation cycle, the MMRM implementation will be installed on our regulatory R platform, too.

Opens the door to submissions including the MMRM results from R.

Further convergence improvements: Discussing e.g. with Ben Bolker from lme4 team on best practice for handling row ordering, convergence warnings, etc. (issue)

This will increase the robustness and user experience further.



Methods Extensions: Additional covariance structures (that are between unstructured and compound symmetry) would be good as fallback solution. Random slope analysis module could leverage backbone pieces.

Will take more time but cover more use cases.

References

Please reach out to daniel.sabanes_bove@roche.com for questions!

NEST

- UseR2020 on rtables: https://www.youtube.com/watch?v=CBQzZ8ZhXLA by G. Becker
- Phuse 2019 and R in Pharma 2018: “Analysing Clinical Trials Data with R” by A. Waddell https://rinpharma.github.io/website2018/program/analyzing-clinical-trials-data-with-r.html

MMRM

- Mallinckrod, C. H., Lane, P. W., Schnell, D., Peng, Y., & Mancuso, J. P. (2008). Recommendations for the Primary Analysis of Continuous Endpoints in Longitudinal Clinical Trials. Drug Information Journal, 42(4), 303–319. https://doi.org/10.1177/009286150804200402

Doing now what patients need next