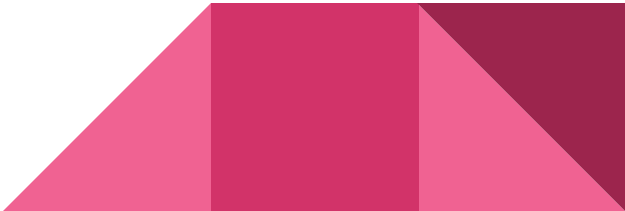


Mixed Model Repeated Measures (MMRM) Analysis Package in R

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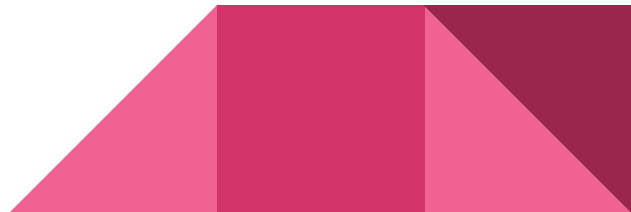


Overview

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Motivation

- Early 2022 when R generated MMRM outputs were to be used as an official quality control for two studies within Ophthalmology at Roche
- Packages attempted to try to create these outputs were *lme4*, *nlme* and *glmmTMB*
- Model convergence issues, unavailability of covariance structures, adjusted degrees of freedom, or numerical results being far from SAS® were problems that were faced with these R packages
- It was then decided that a new package needed to be created to not only allow for convergence on such large datasets but also incorporate other key features that would be needed for study work that these other packages did not have

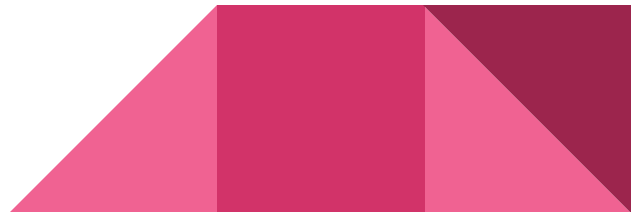


Cov Structure	mmrm	glmmTMB	nlme	SAS
UN	X	X	X	X
ANTE(1)	X			X
TOEPH	X	X	X	X
TOEP	X		X	X
ARH(1)	X		X	X
AR(1)	X	X	X	X
CSH	X	X	X	X
CS	X		X	X

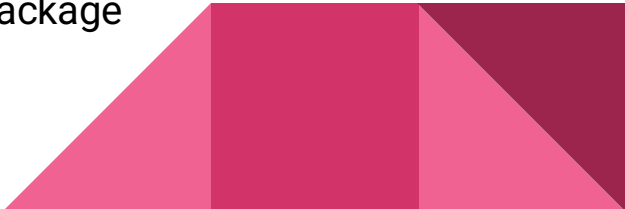
Figure 1: Commonly used covariance structures available by software

Foundation of *mmrm* package

- Based on the marginal linear model without random effects using Template Model Builder (TMB) which enables fast and robust model fitting.
 - allows this package to be at least 3-5 times faster than previous solutions.
- The *mmrm* package supports Restricted Maximum Likelihood (REML) and Maximum Likelihood (ML).
- When producing the model, the package tries multiple optimizers if the default optimizer does not lead to convergence.

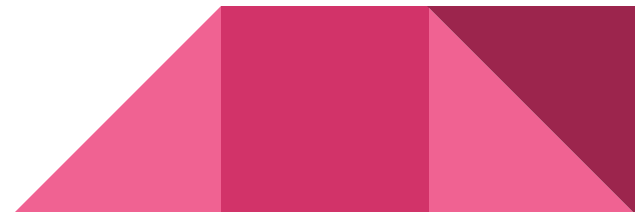


Features

- Variety of covariance matrices (including UN, TOEP, TOEPH, ANTE(1), AR(1), ARH(1), CS and CSH)
 - Weight observations
 - Fit models with restricted or standard maximum likelihood inference
 - Perform hypothesis testing with Satterthwaite or Kenward-Roger adjustment
 - Extract least square means estimates by using the *emmeans* package
- 

Comparison to Other R Packages

- Five completed phase three ophthalmology randomized controlled trials were used for extensive assessment and comparison between the new *mmrm* package and *nlme*, *glmmTMB* and SAS.
 - Note: *lme4* was not included as it would not converge on any of these studies
- Primary endpoint: change from baseline in BCVA scores at pre-defined visits
 - Note: These five studies had already used SAS for their analyses and this work was done to explore how the various R software would compare in results.
- Analysis carried out using `proc mixed` in SAS, the `gls` function in *nlme*, *glmmTMB* in *glmmTMB* and *mmrm* in *mmrm*
- Comparison included whether the model converged, the running time, least square means, contrasts, standard errors and p-values
- Eight different covariance structures were assessed
 - UN, TOEP, TOEPH, ANTE(1), AR(1), ARH(1), CS and CSH



	Study 1	Study 2	Study 3	Study 4	Study 5
<u>mrmr</u>	x	x	x	x	x
<u>glmmTMB</u>	x	x	x	x	x
<u>nlme</u>	x			x	x
SAS	x	x	x	x	x

Figure 2: Convergence of main analysis with UN on all five studies respectively

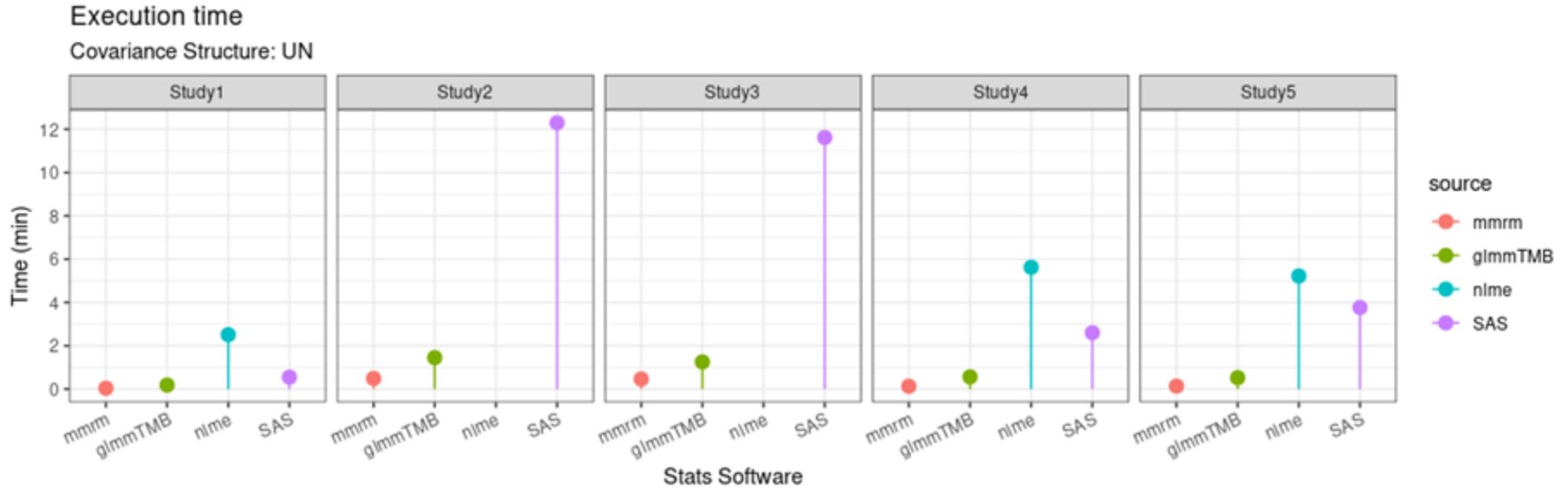


Figure 3: Running time to convergence using MMRM with UN covariance for each of the softwares

MMRM (UN) LSmeans and CI for study visits

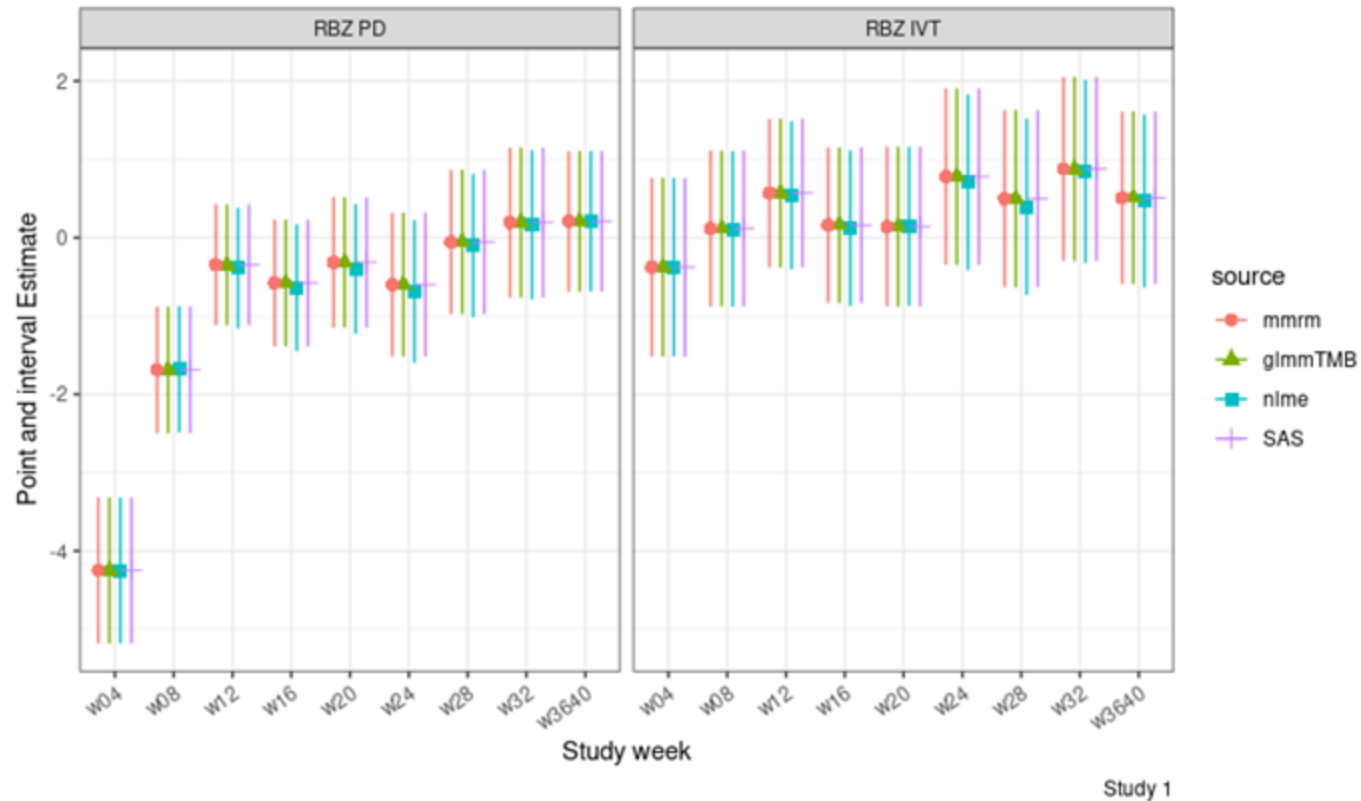


Figure 4: Least Square Means Estimates by software

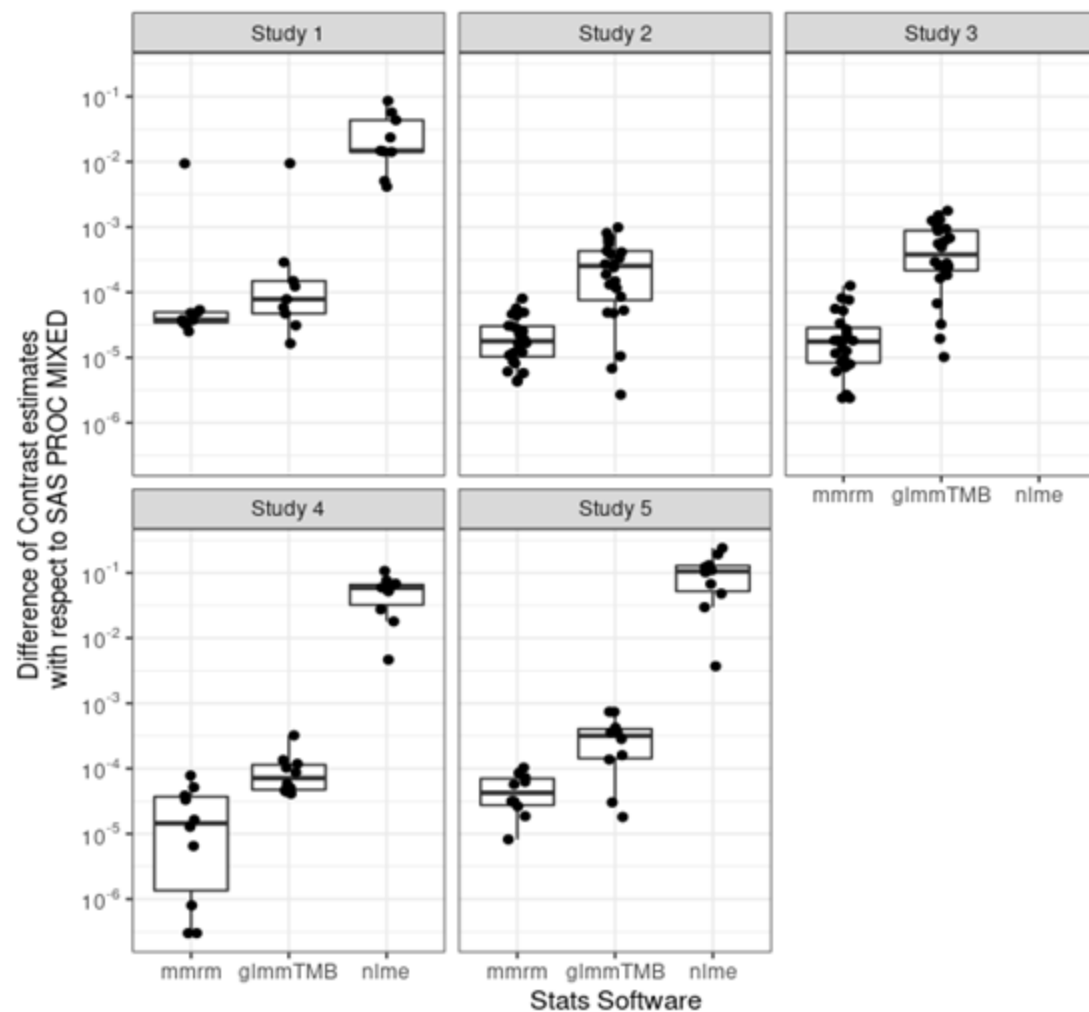


Figure 5: Differences in contrast estimates with respect to SAS where individual data points represent different study visits

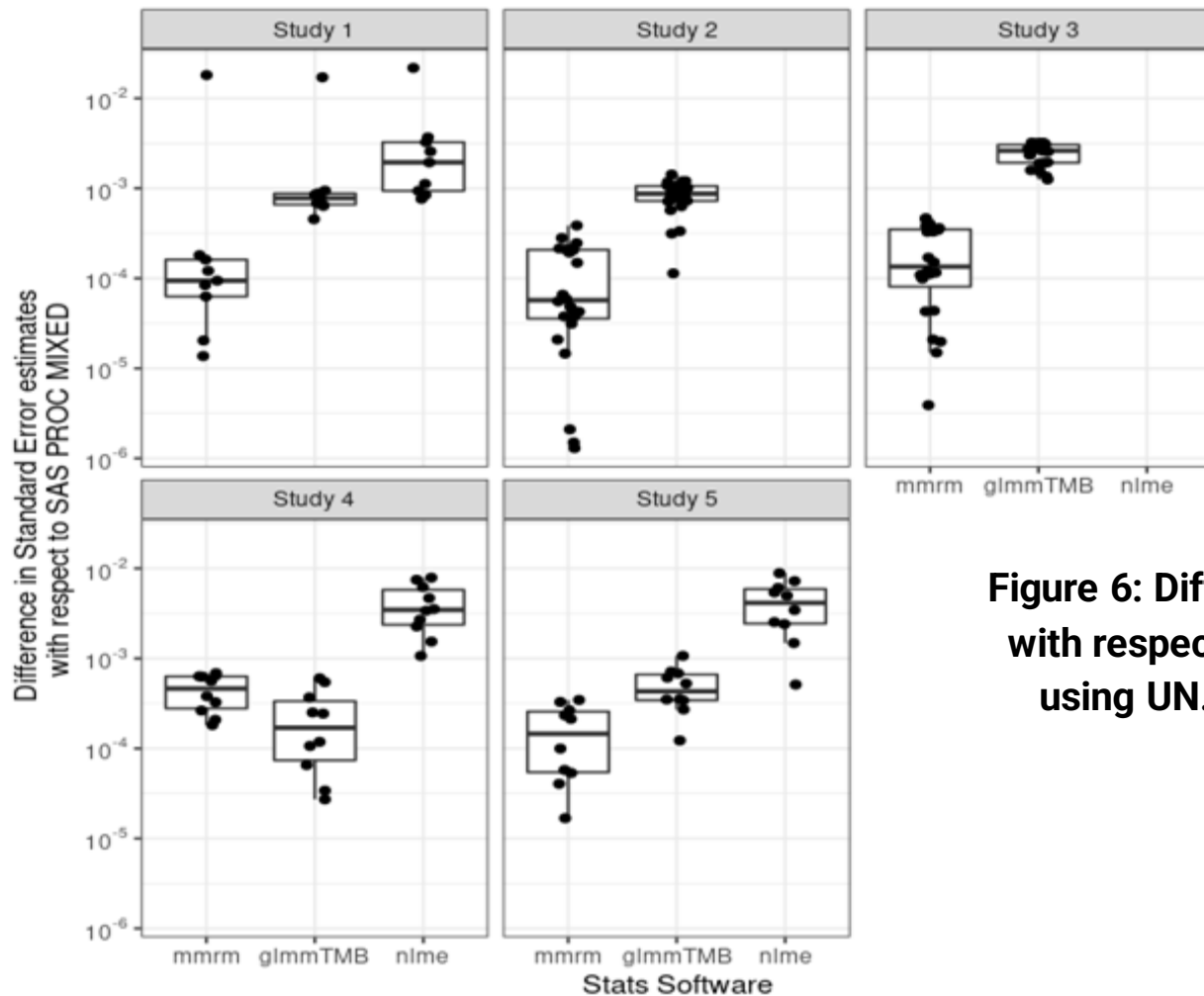


Figure 6: Difference in standard error estimates with respect to SAS for each of the softwares using UN. Individual data points represent different study visits

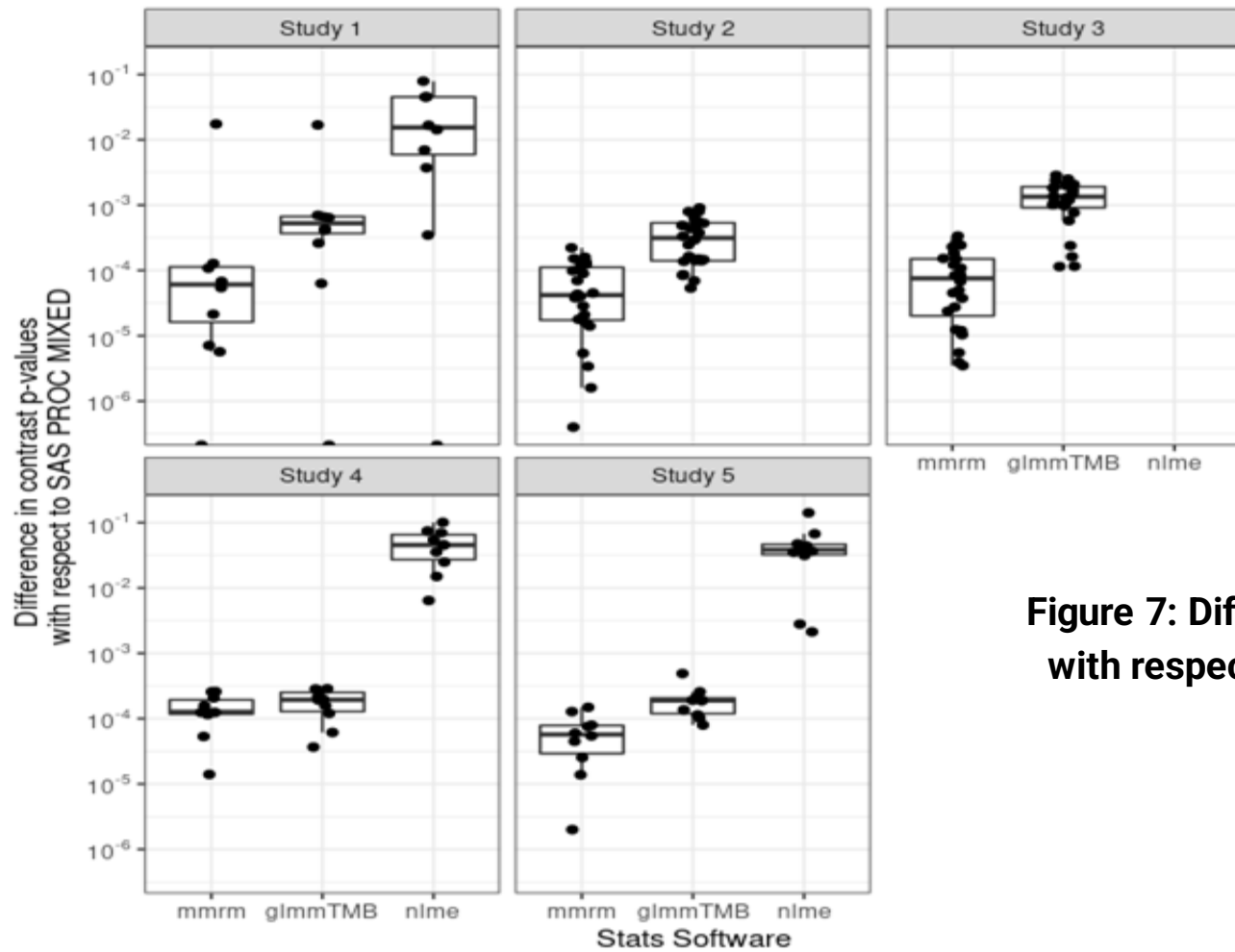
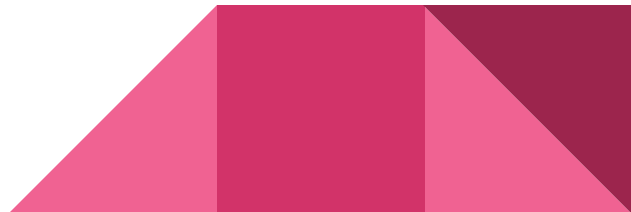


Figure 7: Difference in contrast p-values with respect to SAS for each software

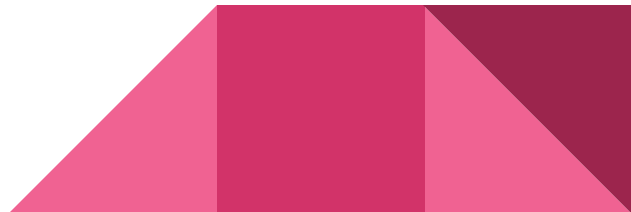
Summary of Comparison Results

- *mrmr* and *glmmTMB* are much faster than *nlme* and SAS, in particular with complex covariance structures (ie. UN, ANTE(1), TOEPH and CSH)
- *mrmr* is consistently faster than *glmmTMB*, converging in less than 30 seconds
- There are no convergence problems with *mrmr* and it has rather small differences from SAS in terms of least square means, contrasts, standard errors and p-values



Advantages of *mmrm*

- The *mmrm* package is the best candidate for an R based package that will converge under a large variety of covariance structures
- *mmrm* has Satterthwaite and Kenward-Roger adjusted denominator degrees of freedom which is important for controlling the type I error rate in the framework of complex mixed-effects models when applied to clinical trial data
- Additional comparisons are still in progress to assess the package against SAS and the American Statistical Association is performing ongoing maintenance and support of the package



How to use *mmrm*

```
library(mmrm)
fit <- mmrm(
  formula = FEV1 ~ RACE + SEX + ARMCD * AVISIT + us(AVISIT|USUBJID),
  data = fev_data
)
```

Formula: FEV1 ~ RACE + SEX + ARMCD * AVISIT + us(AVISIT | USUBJID)
Data: fev_data (used 537 observations from 197 subjects with maximum 4 timepoints)
Covariance: unstructured (10 variance parameters)
Method: REML
Deviance: 3386.45

Coefficients:

(Intercept)	RACEblack or African American	RACEwhite
30.77747548	1.53049977	5.64356535
SEXFemale	ARMCDTRT	AVISITVIS2
0.32606192	3.77423004	4.83958845
AVISITVIS3	AVISITVIS4	ARMCDTRT:AVISITVIS2
10.34211288	15.05389826	-0.04192625
ARMCDTRT:AVISITVIS3	ARMCDTRT:AVISITVIS4	
-0.69368537	0.62422703	

Figure 8: Example code to produce an MMRM model

```
library(emmeans)
mar_means <- emmeans(fit, trt.vs.ctrl ~ ARMCD|AVISIT,
                      weights = "proportional")
```

\$emmeans

AVISIT = VIS1:

ARMCD	emmean	SE	df	lower.CL	upper.CL
PBO	33.0	0.752	145	31.5	34.5
TRT	36.8	0.764	144	35.3	38.3

AVISIT = VIS2:

ARMCD	emmean	SE	df	lower.CL	upper.CL
PBO	37.8	0.608	145	36.6	39.0
TRT	41.6	0.603	143	40.4	42.8

\$contrasts

AVISIT = VIS1:

contrast	estimate	SE	df	t.ratio	p.value
TRT - PBO	3.77	1.074	146	3.514	0.0006

AVISIT = VIS2:

contrast	estimate	SE	df	t.ratio	p.value
TRT - PBO	3.73	0.859	145	4.346	<.0001

Figure 9: Example code to produce marginal means and contrasts from an MMRM model

Acknowledgements

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