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Mixed Model Repeated Measures (MMRM) Analysis Package in R

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ABSTRACT

Mixed models for repeated measures (MMRM) analyses have been extensively used in the pharmaceutical industry. They provide a comprehensive way to analyze longitudinal continuous endpoints of clinical trials with missing values under the missing at random assumption. SAS® has been the gold standard for this analysis, and so far R-packages fall short for one of the following reasons: model convergence issues, unavailability of covariance structures or adjusted degrees of freedom, or numerical results being far from SAS. After an extensive comparative analysis of these shortcomings, a new R package, "mmrm", was developed addressing the aforementioned problems. As a co-author of this new open sourced package, I will go through the fundamentals of the package, provide a detailed comparison to the other MMRM packages currently available, and show the new features only this package offers for MMRM analysis in R.

INTRODUCTION

The motivation for the *mmrm* package came in early 2022 when R generated MMRM outputs were to be used as an official quality control for two studies within Ophthalmology at Roche. The packages that were used to try to create these outputs were *lme4*, *nlme* and *glmmTMB*. However, 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. This is when it was 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. Some of these features include having the Satterthwaite adjusted degrees of freedom as well as many important covariance structures including unstructured (UN), homogeneous Toeplitz (TOEP), heterogeneous Toeplitz (TOEPH) , heterogeneous ante-dependence (ANTE(1)) , auto-regressive (AR(1)) , heterogeneous auto-regressive (ARH(1)), compound symmetry (CS) and heterogeneous compound symmetry (CSH). Rigorous testing of the packages was done on five completed phase 3 studies analyzed in SAS.

Figure 1 shows the most commonly used covariance structures in Ophthalmology and other disease areas available in *mmrm*, *glmmTMB*, *nlme* and SAS.

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

OVERVIEW OF THE NEW *mmrm* PACKAGE AND ITS FEATURES

The *mmrm* package is based on the marginal linear model without random effects using Template Model Builder (TMB) which enables fast and robust model fitting. TMB allows to perform the log-likelihood calculations in C++, which allows this package to be at least 3-5 times faster than previous solutions. The user is able to specify a variety of covariance matrices, weight observations, fit models with restricted or standard maximum likelihood inference, perform hypothesis testing with Satterthwaite or Kenward-Roger adjustment, and extract least square means estimates by using the *emmeans* package. When producing the model, the package tries multiple optimizers if the default optimizer does not lead to convergence. More details on the model fitting algorithm and features can be found on the Open Pharma Github page under the *mmrm* package as well as in the documentation on CRAN. The links to these pages are available in the appendix.

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 that *lme4* was not included as it would not converge on any of these studies. The primary endpoint on these studies was the change from baseline in BCVA scores at pre-defined visits. The comparison was done on the main analysis specified for the primary endpoint as per the studies respective Statistical Analysis Plans (SAPs). Note that 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. This was carried out using proc mixed in SAS, the gls function in *nlme,* glmmTMB in *glmmTMB* and mmrm in *mmrm*. The comparison of these packages using the five studies included whether the model converged, the running time, least square means, contrasts, standard errors and p-values. The analyses were performed using eight different covariance structures: unstructured, homogeneous Toeplitz, heterogeneous Toeplitz, heterogeneous ante-dependence, auto-regressive, heterogeneous auto-regressive, compound symmetry and heterogeneous compound symmetry.

Figure 2 shows the convergence of the main analysis on the five studies with an unstructured covariance for each of the softwares. Notice that there was no convergence with *nlme* in the two larger studies (denoted by the red box in **Figure 2**).

	Study 1	Study 2	Study 3	Study 4	Study 5
mmrm	x	x	x	x	x
glmmTMB	x	x	x	x	x
nlme	x			x	x
SAS	x	x	x	x	x

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

Note that this was also the case with other covariance structures and other packages but what remained consistent is that the *mmrm* package always achieved convergence for these studies with each covariance structure.

Figure 3 shows the running time for each software using UN to produce the model.

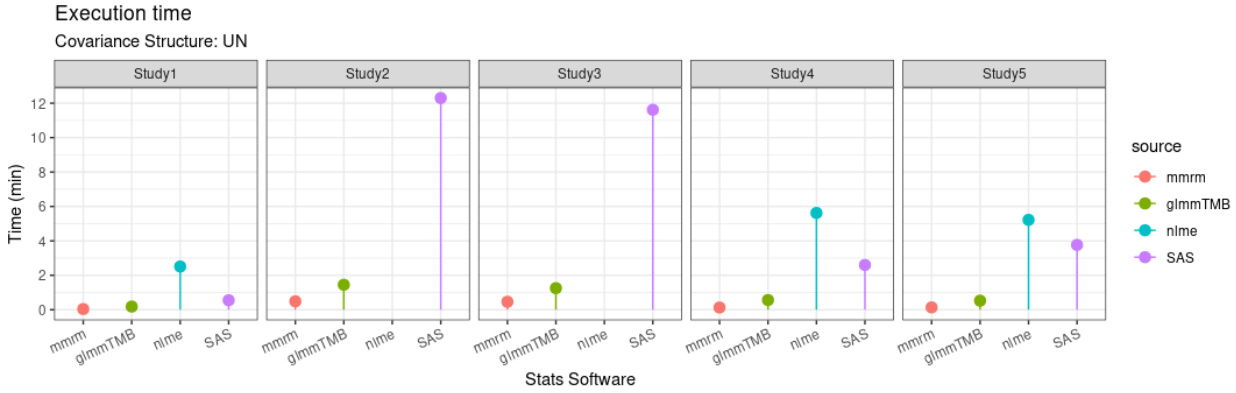

Figure 3: Running time to convergence using MMRM with UN covariance for each of the softwares

Notice that *mmrm* is the fastest, notably even faster than *glmmTMB*. On average, *mmrm* converged for each of the studies in less than 30 seconds. Similar results were achieved with other covariance structures for each of the softwares.

Figure 4 shows the Least Square Means estimates between the different softwares for study one using UN. Similar results were obtained for the other four studies and hence, have been omitted in this paper.

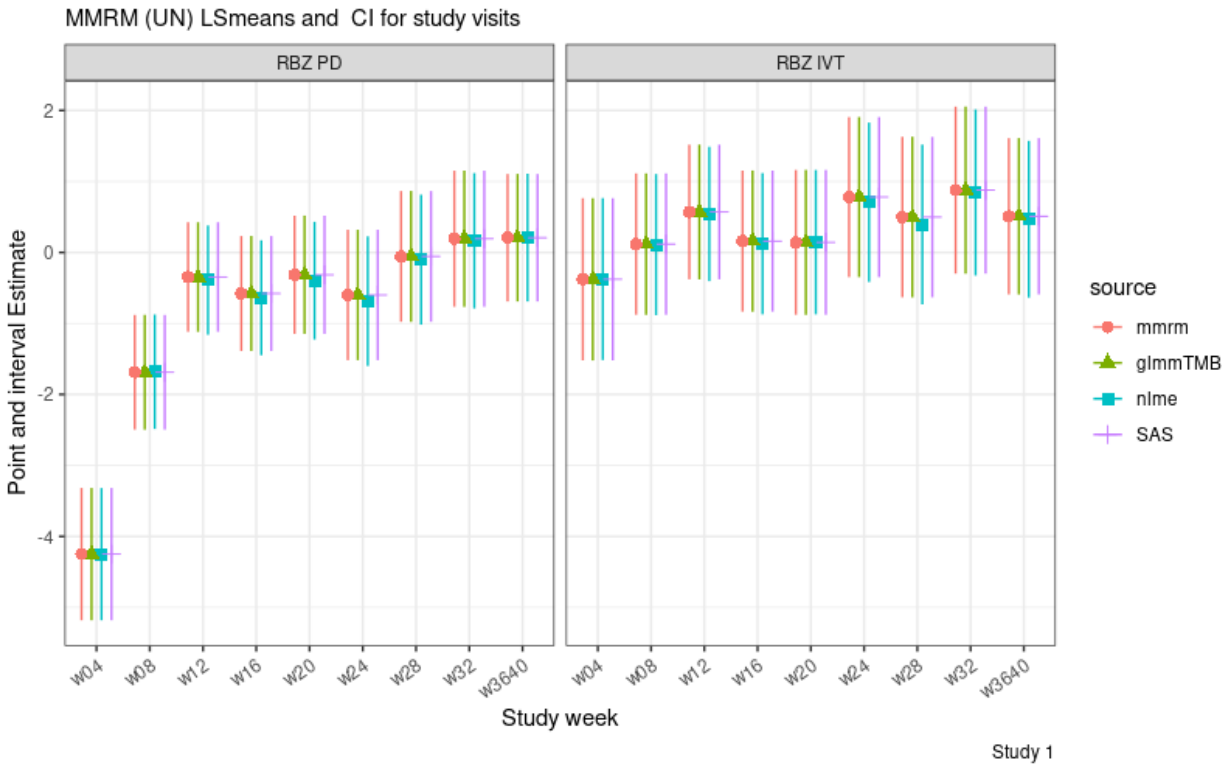

Figure 4: Least Square Means Estimates by software

Notice that *nlme* is clearly the most different from SAS. *mmrm* has results closest to SAS amongst the R packages. This was also the case for other covariance structures. **Figure 5** gives a summary of the differences in contrast estimates for the five studies with respect to SAS using UN.

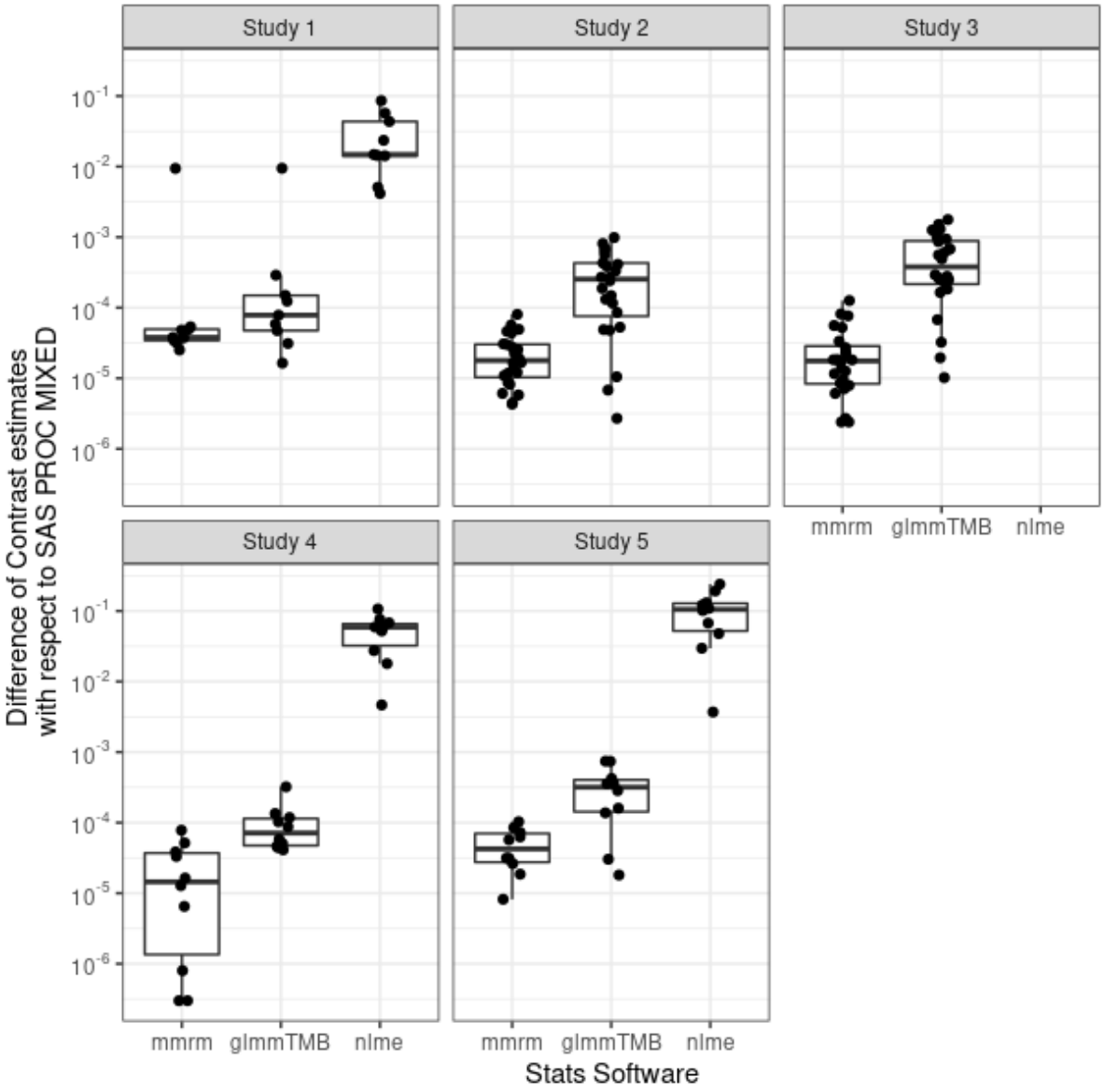

Figure 5: Differences in contrast estimates with respect to SAS where individual data points represent different study visits

Notice that the *mmrm* package is closest to the SAS results. Depending on the imbalance of data (ie. study one), it is approximately 1 order of magnitude closer. **Figure 6** shows the difference in standard error estimates with respect to SAS for each of the five studies.

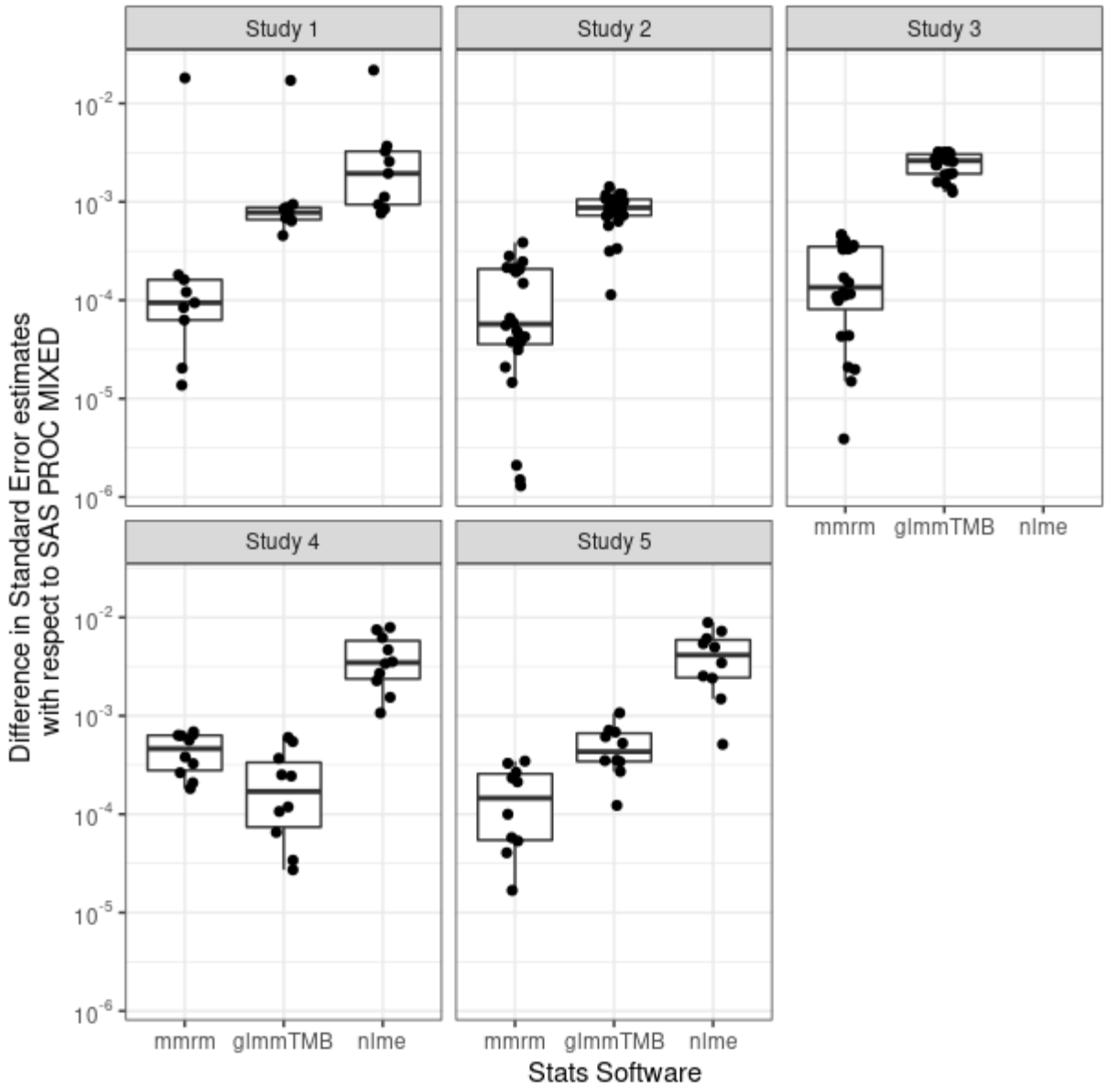

Figure 6: Difference in standard error estimates with respect to SAS for each of the softwares using UN. Individual data points represent different study visits

Notice that *mmrm* is generally closest to the SAS results for all studies. Depending on the data imbalance, *mmrm* is approximately one order of magnitude closer to SAS. This was the case with all other covariance structures. **Figure 7** shows differences in p-values of study contrasts with respect to SAS using UN.

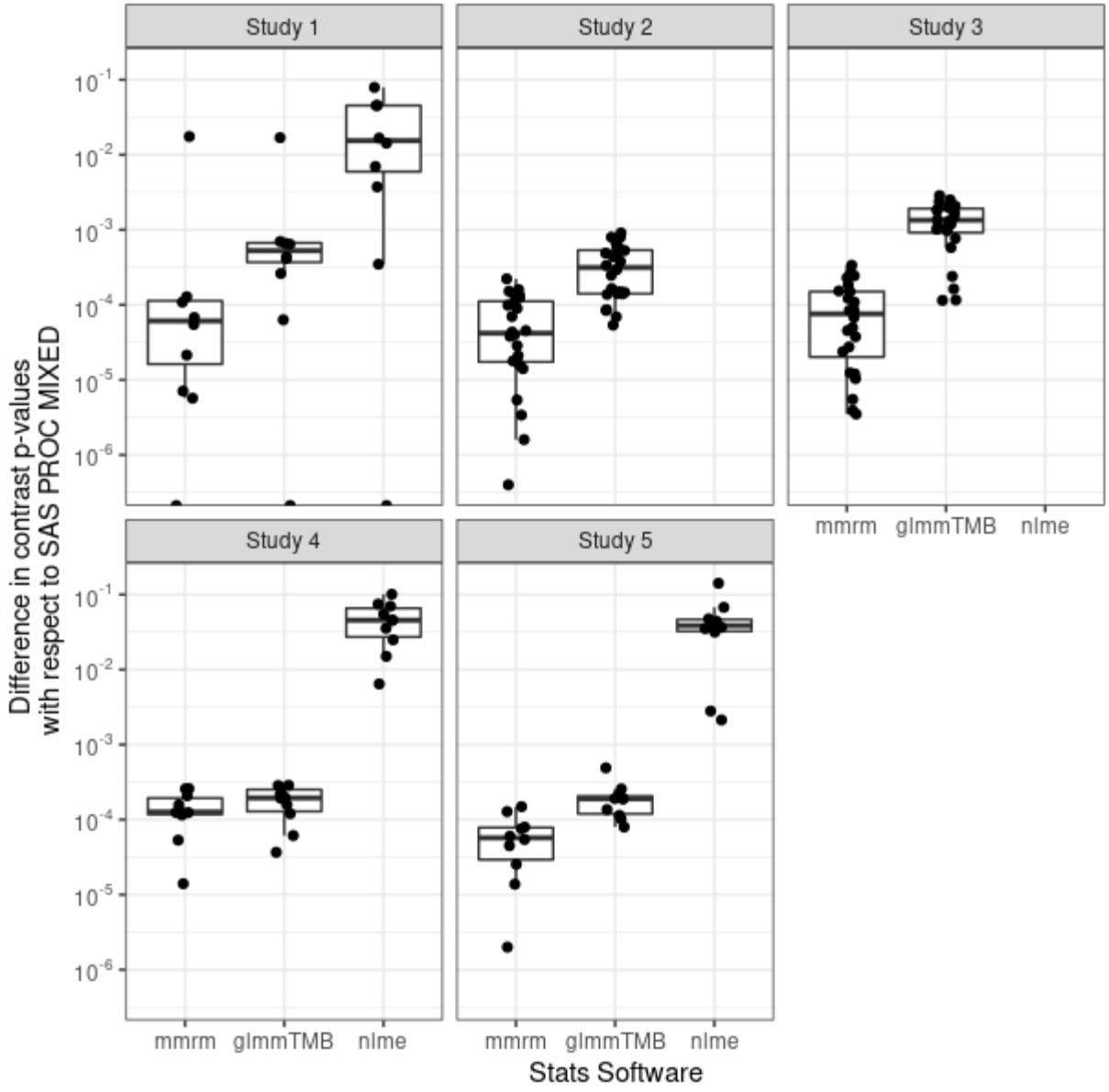

Figure 7: Difference in contrast p-values with respect to SAS for each software

Notice that the difference in contrasts is closest for *mmrm* and in particular, it is approximately one order of magnitude smaller than *glmmTMB.*

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

HOW TO USE *mmrm* AND ITS ADVANTAGES

As shown, the *mmrm* package is the best candidate for an R based package that will converge under a large variety of covariance structures. It is also worth noting that *nlme* and *glmmTMB* do not give Satterthwaite or 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.

The package is very easy to use and there is a lot of documentation with examples on how to use it. To get started, an example dataset can be called within the package known as “fev_data”. **Figure 9** is an example of how to produce an MMRM model on the example dataset.

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

Figure 8: Example code to produce an MMRM model

The code in **Figure 8** specifies an MMRM with the given covariates (RACE and SEX) and an unstructured covariance matrix for the time points (the visits given by AVISIT) within the subjects (USUBJID). Calling the function summary() will provide the coefficient table with Satterthwaite degrees of freedom as well as the covariance matrix estimate.

The code in **Figure 9** shows how to obtain the marginal means for each treatment group (ARMCD) at each time point (visits in the AVISIT variable). It also allows for contrasts to be obtained.

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

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

CONCLUSION

As seen through the comparison of five large phase three ophthalmology randomized controlled trials, model convergence, availability of covariance structures and different numerical results from SAS are no longer a problem with the *mmrm* R package. The speed at which these models are produced is also the quickest amongst the available R packages. As we shift towards using different softwares in the pharmaceutical industry, it is important to have reliable and flexible means to conduct our analyses. With the movement towards open source technologies, such as R, allowing for this flexibility, we are able to implement and explore solutions that were not available in the past. It is with packages like *mmrm* that will allow us to strive for excellence in our clinical trials.

REFERENCES

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