ReplicateBE

Software Validation Report

Version: ≥ 1.1.0

Type: Julia package

Repository: https://github.com/PharmCat/ReplicateBE.jl

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1. Description

ReplicateBE provides mixed model solution for replicate designed bioequivalence study. This can be used to obtained results with methods C (random effects with interaction), given by the EMA in Annex I. Statistical model formed with accordance FDA Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, APPENDIX F.

2. Details

The solution to the mixed model equations is a maximum likelihood estimate when the distribution of the errors is normal. PROC MIXED in SAS used restricted maximum likelihood (REML) approach by default (Henderson, 1959;Laird et.al. 1982; Jennrich 1986; Lindstrom & Bates, 1988; Gurka et.al 2006).

In *ReplicateBE* finding solution for minimization -2logL(θ) respectively to θ done with Newton's family methods with *Optim* package. In some cases post-optimization step can be performed with Broyden–Fletcher–Goldfarb–Shanno method ((L)-BFGS)(Fletcher & Roger, 1987; Wright, 2006). Because variance have only positive values and ρ is limited as $-1 \leq \rho \leq 1$ in CSH (SAS implementation) and $0 \leq \rho \leq 1$ in *ReplicateBE* by default the "linking" function is used. Exponential values is optimizing in variance part and ρ is linked by sigmoid function.

All steps perform with differentiable functions with forward automatic differentiation using *ForwardDiff* package. *ForwardDiff* is a Julia package for forward-mode automatic differentiation (AD) featuring performance competitive with low-level languages like C++. Unlike recently developed AD tools in other popular high-level languages such as Python and MATLAB, *ForwardDiff* takes advantage of just-in-time (JIT) compilation to transparently recompile AD-unaware user code, enabling efficient support for higher-order differentiation and differentiation using custom number types (including complex numbers). The field of automatic differentiation provides methods for automatically computing exact derivatives (up to floating-point error) given only the function itself (Revels et al., 2016; Mogensen et al., 2018).

3. Requirements

Julia version 1.0 – 1.2 installed.

4. Installation

```
using Pkg; Pkg.add("ReplicateBE")
```

5. Testing

```
using Pkg; Pkg.test("ReplicateBE")
```

6. Validation

6.1 Reference software

ReplicateBE results was compared with results obtained in IBM SPSS v25. SPSS code:

```
MIXED var BY sequence period formulation
 /CRITERIA=CIN(90) MXITER(8000) MXSTEP(200) SCORING(1) SINGULAR(0.0000000000001) HCONVERGE(0,
   ABSOLUTE) LCONVERGE(0, ABSOLUTE) PCONVERGE(0.000000001, ABSOLUTE)
 /FIXED=sequence period formulation  | SSTYPE(3)
 /METHOD=REML
 /PRINT=G
 /RANDOM=formulation | SUBJECT(subject) COVTYPE(CSH)
 /REPEATED=formulation | SUBJECT(subject*period) COVTYPE(DIAG)
 /EMMEANS=TABLES(formulation) COMPARE ADJ(LSD).
```

6.2 Validation program

- 24 subjects, sequence balanced dataset
  - TRTR/RTRT
  - TRRT/RTTR
  - TTRR/RRTT
  - TRT/RTR
- 48 subjects, sequence unbalanced, 20 randomly dropped observations
  - TRTR/RTRT
  - TRRT/RTTR
  - TTRR/RRTT
  - TRT/RTR
- 36 subjects, sequence unbalanced dataset
  - TRTR/RTRT
  - TRT/RTR
- 128 subjects, sequence unbalanced dataset
  - TRTR/RTRT
  - TRT/RTR
- 512 subjects, sequence unbalanced dataset
  - TRTR/RTRT
  - TRT/RTR
- 1024 subjects, sequence unbalanced, 2000 randomly dropped observations
  - TRTR/RTRT
- 4096 subjects, sequence unbalanced, 2000 randomly dropped observations
  - TRT/RTR

6.3 Datasets

Datasets can be found in *ReplicateBE* repository.

CSV: https://github.com/PharmCat/ReplicateBE.jl/tree/master/validation/csv

SAV: https://github.com/PharmCat/ReplicateBE.jl/tree/master/validation/sav

6.4 Results

Dataset	Design	Subjects	Exp90CI Lower SPSS	Exp90CI Upper SPSS	-2REML SPSS	-2REML RBE	Exp90CI Lower RBE	Exp90CI Upper RBE	Dev Exp90CI Lower	Dev Exp90CI Upper	Dev -2REML	Conformity
RDS1	TRTR/RTRT	24	0.800182	1.208955	164.613360	164.6134	0.8002	1.2090	0.0000	0.0000	0.000000	YES
RDS2	TRRT/RTTR	24	0.877858	1.266491	197.200371	197.2004	0.8779	1.2665	0.0000	0.0000	0.000000	YES
RDS3	TTRR/RRTT	24	0.838738	1.132936	149.254935	149.2549	0.8387	1.1329	0.0000	0.0000	0.000000	YES
RDS7	TRT/RTR	24	0.824266	1.269283	138.044846	138.0448	0.8243	1.2693	0.0000	0.0000	0.000000	YES
RDS12	TRTR/RTRT	48	0.922325	1.183449	329.764543	329.7645	0.9223	1.1834	0.0000	0.0000	0.000000	YES
RDS13	TRRT/RTTR	48	0.910963	1.187195	305.219589	305.2196	0.9110	1.1872	0.0000	0.0000	0.000000	YES
RDS14	TTRR/RRTT	48	0.937277	1.205799	277.976236	277.9762	0.9373	1.2058	0.0000	0.0000	0.000000	YES
RDS19	TRR/RTT	48	0.775474	1.091712	255.995363	255.9954	0.7755	1.0917	0.0000	0.0000	0.000000	YES
RDS23	TRTR/RTRT	36	0.638039	1.135006	252.044906	252.0449	0.6380	1.1350	0.0000	0.0000	0.000000	YES
RDS24	TRT/RTR	36	0.854985	1.293459	140.107149	140.1071	0.8550	1.2935	0.0000	0.0000	0.000000	YES
RDS26	TRTR/RTRT	128	0.618915	0.772626	899.044672	899.0447	0.6189	0.7726	0.0000	0.0000	0.000000	YES
RDS27	TRT/RTR	128	1.186962	1.433490	614.340739	614.3407	1.1870	1.4335	0.0000	0.0000	0.000000	YES
RDS28	TRTR/RTRT	512	0.697535	0.769849	3495.580039	3495.5800	0.6975	0.7698	0.0000	0.0000	0.000000	YES
RDS29	TRT/RTR	512	1.361488	1.498934	2540.296180	2540.2962	1.3615	1.4989	0.0000	0.0000	0.000000	YES
RDS101	TRTR/RTRT	1024	0.872242	0.943798	4121.783115	4032.9198	0.8687	0.9375	-0.0035	-0.0063	-88.863295	NA*
RDS102	TRT/RTR	4096	0.357036	0.382583	26633.16439	26633.1644	0.3570	0.3826	0.0000	0.0000	0.000000	YES

*SPSS WARNING: The final Hessian matrix is not positive definite although all convergence criteria are satisfied. The MIXED procedure continues despite this warning. Validity of subsequent results cannot be ascertained. ReplicateBE fitting is better (less -2REML).

7. Conclusion

ReplicateBE corresponds to reference software under the validation program.

8. Other

Package documentation:

https://pharmcat.github.io/ReplicateBE.jl/latest/

Validation documentation:

https://github.com/PharmCat/ReplicateBE.jl/tree/master/validation

Details:

https://www.researchgate.net/publication/336829970_ReplicateBE_linear_mixed_effect_model_solution_for_replicated_bioequivalence_design_with_accordance_to_FDA_guideline_EMA_model_type_C

9. Literature

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