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Practical considerations for using the full random effects modeling (FREM) approach to covariate modeling

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Objectives

The aim of this work is to investigate practical usage considerations of FREM including the estimation method(s), specification of different parameterizations of the parameter-covariate relationships and the sensitivity to the additional distributional assumptions required by FREM.

Background

- The FREM approach to covariate modeling has been suggested to avoid issues with standard covariate model building approaches, e.g. selection bias[1,2]
- Implemented in PsN[3] and similar to the full fixed effects modeling (FFEM) approach (all parameter-covariate relationships are estimated simultaneously), but through covariance instead of structural effects
- Advantages over FFEM; e.g. with missing data, correlated covariates[4]
- Allows conditional interpretation of the results, i.e. coefficients and variability conditional on only a subset of covariates (even a single covariate) without having to re-fit the final model
- FREM has an unusual implementation of the covariate model with implicit covariate effect relations

Conclusion

The investigation gives information to implementation of FREM with respect to practical aspects such as estimation method, parameterizations, expected performance and robustness towards covariate distribution. Further, it supports FREM for unbiased covariate confirmatory analyses.

Data and Methods

- A simulation study (n=150) in NONMEM was performed, based on real data and the final parameters of a docetaxel model for neutrophil counts[5]. All 18 covariate-parameter relationships were re-estimated with FFEM and FREM using IMPMAP and FOCE. Bias, precision, termination and run-time were evaluated.
- Covariate correlations were low in data (< 40%)
- Implementation details of parameterizations of covariate-parameter relations in FREM were investigated. Both transformation of covariate observations and the FREM model were tested.
- Univariate FFEM coefficients (FFEM with only one covariate per execution) were compared to FREM coefficients
- Non-normal covariate models were tested

Results

- IMPMAP was found more stable than FOCE (FREM successful minimization: 100%, 62%)
- Bias and precision of the re-estimated covariate parameters were similar, as were mean run-times (FOCE 16 cores: 14 min, 30 min; IMPMAP 8 cores: 40 min, 90 min)
- While modeling covariates as random effects, FREM provided accurate covariate coefficients also for non-normal covariate distributions
- Parameterization corresponding to different parameter-covariate relationships could be implemented as either data or model transformations with the same result (Figure 1)
- FREM allowed both univariate (Figure 2) and multivariate (Figure 3) interpretation of the covariate effects simultaneously. When the same relations as FFEM were selected the results were in close agreement.

Parameter model	FREM covariate model (or covariate data): Normal	FREM covariate model (or covariate data): Log-normal
Normal	$P = \theta + (C - \overline{C})\beta + \eta$	$P = \theta + (\ln C - \overline{\ln C})\beta + \eta$
Exponential	$P = \theta e^{(C-\overline{C})\beta+\eta}$	$P = \theta \left(\frac{C}{C_{\mathrm{GM}}}\right)^{\beta} e^{\eta}$

Figure 1. *Interaction of parameter and covariate model on implicit covariate relation parameterization. P, individual parameter model; β, coefficient of covariate effect; C, individual covariate; $\overline{C}$, mean of covariate; C_{GM}, geometric mean of covariate; $\overline{\ln C}$, mean of log-transformed covariate.*

FREM coefficients

	AAG
BASE	0.372
MTT	−0.0246
SLOPE	−0.506

FFEM coefficients

	AAG
BASE	0.372
MTT	−0.0249
SLOPE	−0.507

FREM unexplained variability

	BASE	MTT	SLOPE
BASE	0.121		
MTT	−0.00356	0.0226	
SLOPE	−0.0247	0.0155	0.150

FFEM unexplained variability

	BASE	MTT	SLOPE
BASE	0.122		
MTT	−0.00357	0.0226	
SLOPE	−0.0239	0.0160	0.149

Figure 2. *Illustrative example of FREM results (blue, left) calculated to be interpreted as univariate FFEM results (red, right), i.e. an effect only conditional on knowledge of a single covariate.*

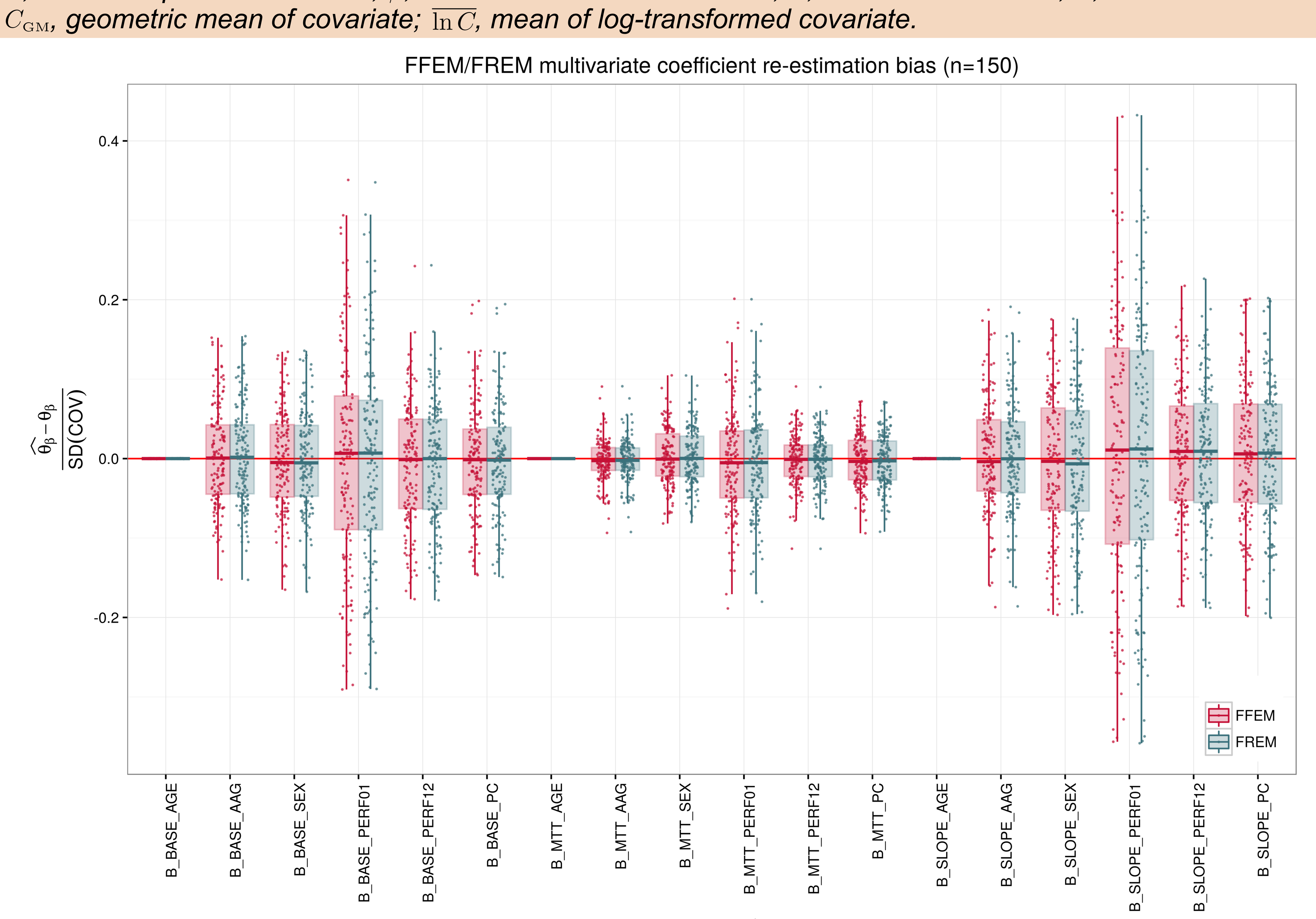

Figure 3. *Estimation bias (absolute bias normalized by covariate standard deviation) of FFEM and FREM coefficients (multivariate; conditional on all) in simulation (n=150) of 6 covariates and 3 parameters, utilizing IMPMAP in NONMEM 7.3 to re-estimate both FFEM and FREM.*

References

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Acknowledgments

The authors are thankful to Merck & Co., Inc. and Malidi Ahamadi for financial and scientific support