Evaluation of FREM and FFEM including use of model linearization

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Background

In full model approaches, covariate relations are predefined [1]. Attaching covariate relations selectively to only some of the model parameters can lead to selection bias [2,3]. By allowing all covariates of interest to affect all parameters, this risk of selection bias is mitigated.

Objectives

We evaluate and compare two full model approaches that both allow estimation of all parameter-covariate relations: a full random effects model (FREM [3,4]) and a full fixed effects model (FFEM) saturated with respect to parameter-covariate relations.

Methods

Dataset

A dataset containing 636 individuals, 3549 observations of neutrophil concentrations after docetaxel administrations, five covariates (AGE, SEX, α_1-acid glycoprotein (AAG), previous chemotherapy (PC) and performance score (PERF)) was used [5]. Categorical covariate PERF which was originally multivariable was treated as dichotomous. In addition, two dummy covariates having correlations of 0.5 (NCOV1) and 0.75 (NCOV2) respectively with a clinically relevant covariate were generated to investigate the performances of FREM and FFEM in case of correlated covariates.

Model

A semi-mechanistic myelosuppression model with four structural parameters (Baseline (BA), Mean transition time (MT), Slope (SL) and Power (PO) was used [5].

Methodology

FREM and FFEM were implemented based on real or real and dummy covariates, respectively. The following aspects were evaluated:

- Confidence intervals for covariate effects
- Run times of non-linear models using bootstraps (n=20, same cluster node).
- VPCs performance (n=1000).
- Linearization to decrease run times during model development and evaluation [6,7].
- Precision of parameter-covariate coefficients using bootstraps (n=1000) based on linearized model.

Results

Run times of the model in FFEM and FREM

The non-linear FFEM and FREM had similar run times, 7.3±1.0 h/run and 7.5±0.8 h/run, respectively.

Linearization

The run times of linearized FFEM and FREM (~10 mins) were substantially shorter than corresponding non-linear models. The ΔOFV of non-linear and linearized models agreed well in both cases.

Clinical relevance

FFEM and FREM identified the same parameter-covariate relationships (AAG on BA and SL) to be clinically relevant (Figure 1).

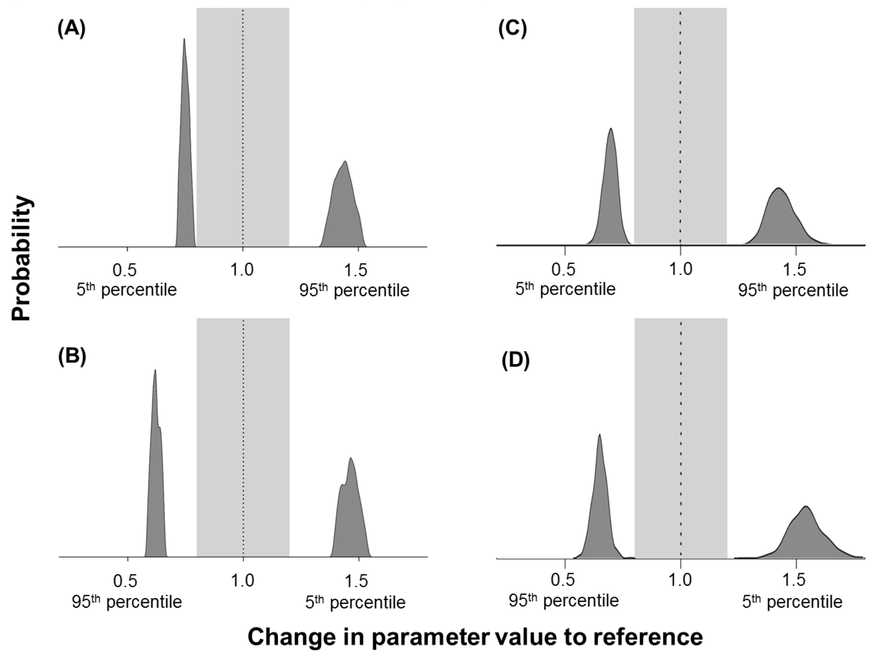

Fig. 1: Clinical relevance plot of BA-AAG (A), SL-AAG (B) in FFEM and BA-AAG (C), SL-AAG (D) in FREM

VPC

VPCs for FFEM and FREM were equal (Figure 2).

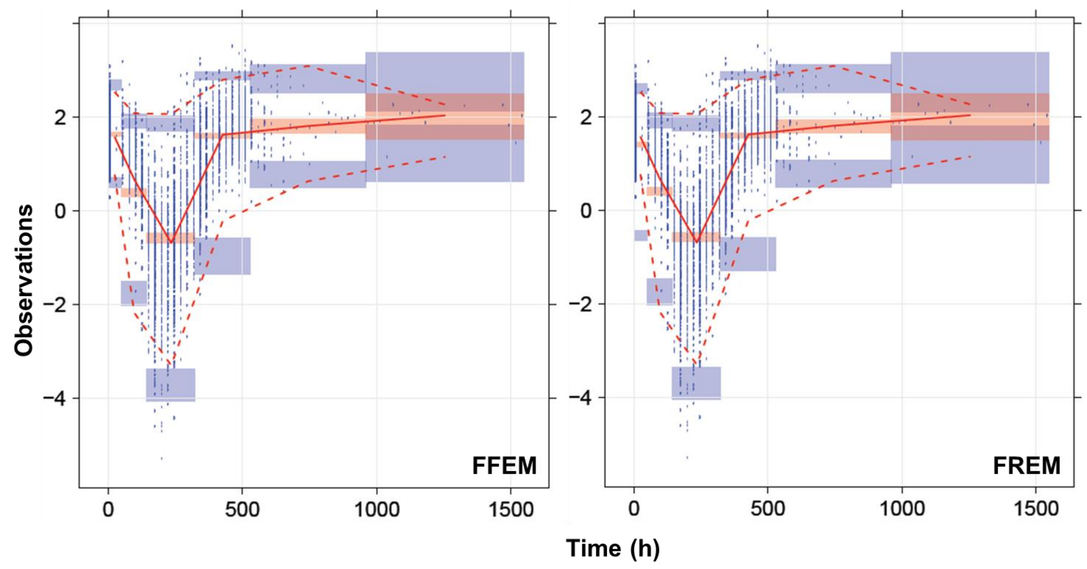

Fig. 2: VPC plots (n=1000)

Precision of parameter-covariate coefficients

FREM was found to estimate coefficients for correlated covariates more precisely than FFEM. The methods estimated uncorrelated covariates with similar precision (Figure 3).

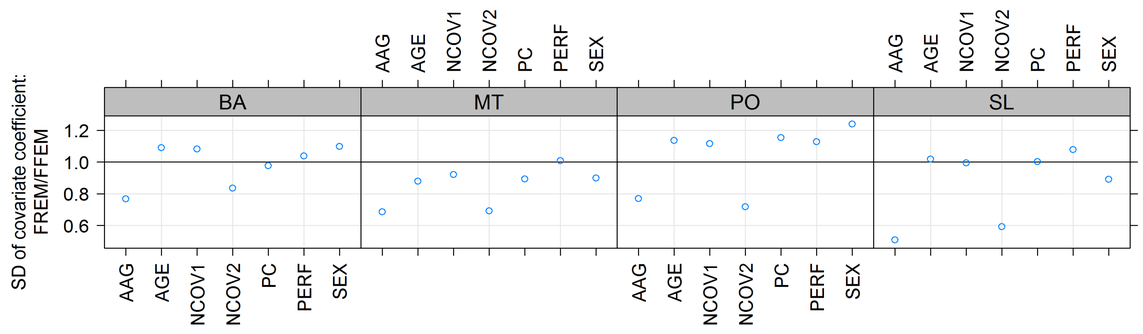

Fig. 3: Relative precision of parameter-covariate coefficients ($SD_{(coef,FREM)}/SD_{(coef,FFEM)}$)

References

[1] Gastonguay, The AAPS Journal 2004 (6), S1, W4354.
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Conclusions

FREM and FFEM performed equally well in the case with an informative dataset and predominantly uncorrelated covariates, FREM showed advantages in comparison with FFEM when characterizing relations in presence of correlated covariates. This first combination of linearization and FREM/saturated FFEM appears to be promising and should be further evaluated.

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