A full model approach based on the covariance matrix of parameters and covariates

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Background

A full fixed effects model (FFEM) approach has been presented [1,2] where parameter-covariate relations of interest to characterise are pre-defined and added into the model as fixed effects. Advantages include no data-driven model selection and rapid model building. Disadvantages include sensitivity to correlated covariates and that non-included parameter-covariate relations may bias estimates of included relations [3]. A new approach based on a full random effects model (FREM) is proposed here to mitigate these drawbacks.

Full Random Effects Model (FREM)

In the FREM covariates enter as observed variables and their distribution are modelled as random effects. A full covariance matrix between random effects for parameters and covariates is estimated together with the other model components. The residual error magnitude for covariates can be fixed to a low value for the standard assumption of error-free covariates. Coefficients for covariate-parameter relations are obtained from the ratio of covariance between parameter and covariate variability to the covariate variance.

Simulation example 1

The method was assessed using simulated data where covariate-parameters were defined as fixed effects with exponential parameterisation in a one-compartment linear PK model with bolus input. Analyses were made using both FFEM and FREM as well as corresponding base models without covariate-parameter relations. Number of subjects and number of covariates and correlation between covariates were varied across simulation conditions. NONMEM 7.1.2 was used for simulations and estimations.

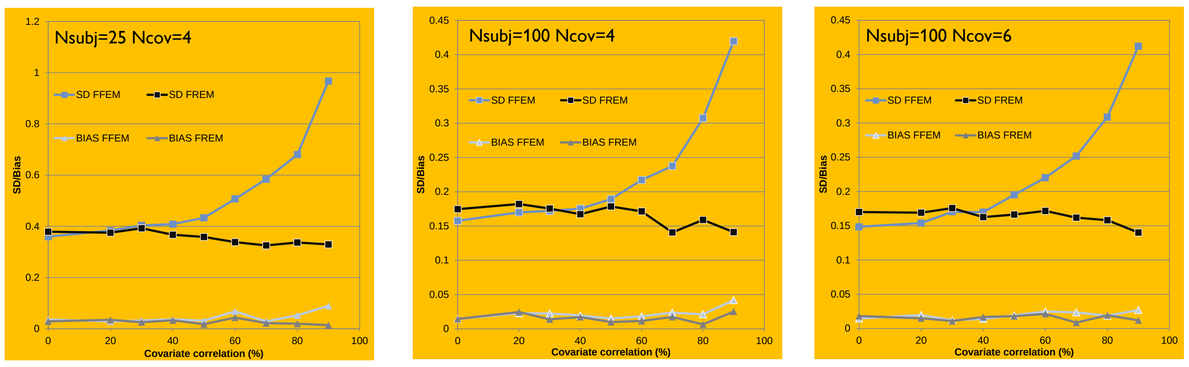

Fig. 1: Result: Average SD and |bias| across covariate coefficients from 100 simulated data set for each condition.

Imprecision in FFEM, but not FREM, estimates increased with increasing covariate correlations. The decrease in OFV was the same for FFEM and FREM upon inclusion of covariates for all conditions (not shown).

Real data set

Pharmacokinetic data following a single oral dose of moxonidine to 74 patients was modeled using a first-order absorption with lag-time and a one-compartment disposition with linear elimination [4]. IIV was implemented for CL, V and ka using a full covariance matrix.

Seven covariates were present in the data set, 3 continuous (AGE, WT, CLCR) and 4 bivariate (SEX, NYHA, ACE, DIG). Correlated (|r|>0.25) covariates were WT-CLCR (0.69), WT-SEX (0.47), and AGE-CLCR (0.47).

FFEM and FREM with 21 covariate-parameter relations were applied to the real data and compared to corresponding base models without covariate relations.

References

[1] Gastonguay The AAPS Journal. 2004 (6), S1, W4354.
[2] Gastonguay PAGE 20 (2011) Abstr 2229
[3] Ivaturi et al. PAGE 20 (2011) Abstr 2228
[4] Karlsson et al. J Pharmacokinet Biopharm. 1998;26(2):207-46

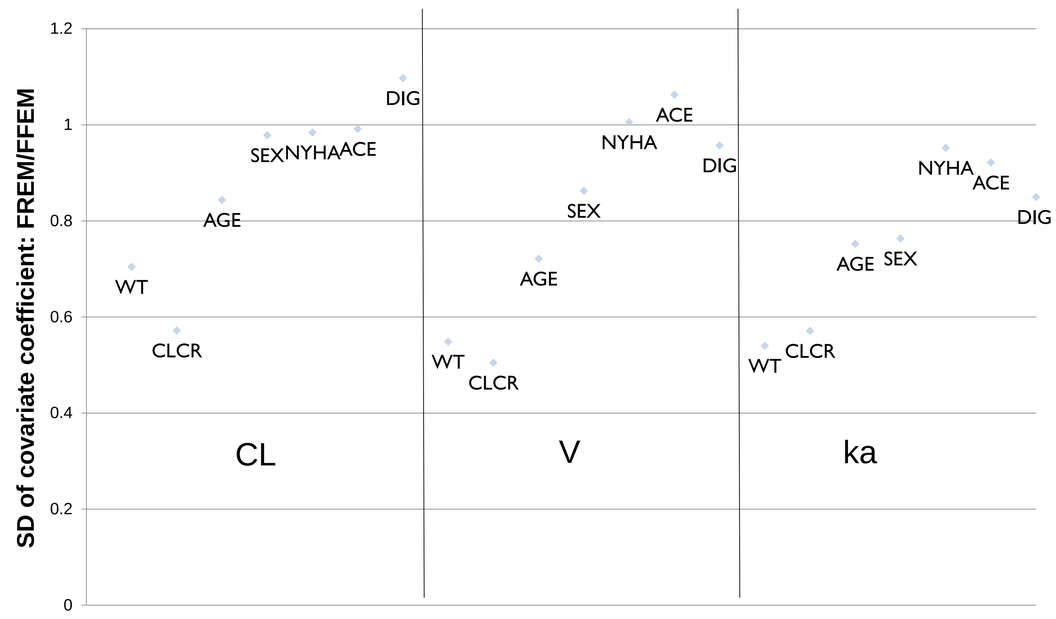

Fig. 1: Imprecision of FREM covariate coefficient estimates relative to FFEM based on 200 bootstrap samples of the real moxonidine data.

Imprecision in FFEM, was higher than for FREM for correlated covariates. The decrease in OFV was the same for FFEM and FREM upon inclusion of covariates (not shown).

Simulation example 2

The final moxonidine FFEM model above was used to simulate 100 new data sets according to the original design and covariate distribution. Each simulated data set was analysed using: (i) FFEM (true model; 21 covariate relations), (ii) FREM (21 relations), (iii) FFEM non-saturated #1-3 (6 pre-defined relations each), (iv) base models including no covariate relations.

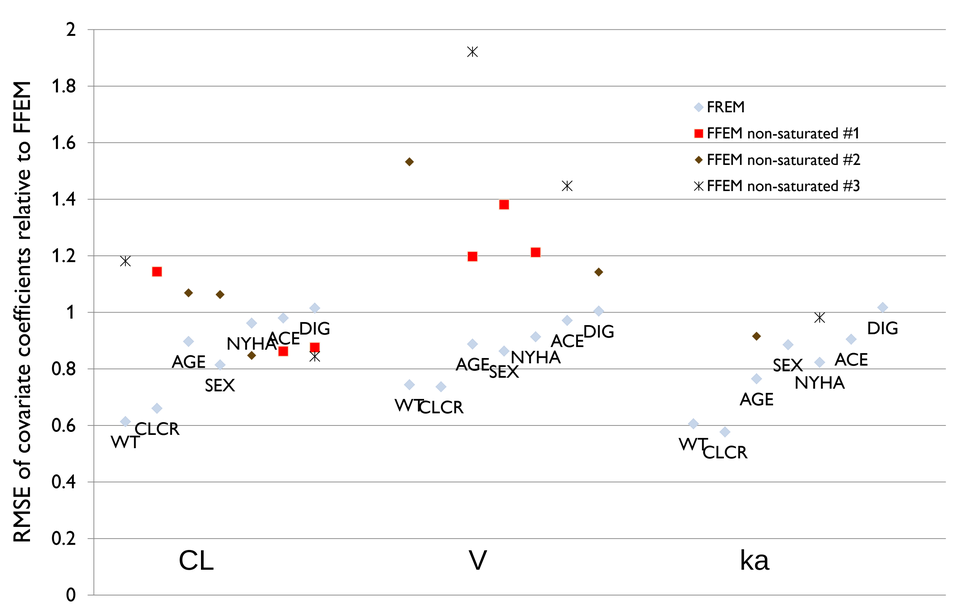

Fig. 2: RMSE for simulated moxonidine data. elative precision of covariate coefficients from 200 bootstrap samples of the real moxonidine data set.

FREM estimates showed highest precision, particularly for covariates with high correlations. The common strategy of pre-defining a subset of covariate-parameter relations (FFEM non-saturated) often led to biased parameters with high RMSE.

Conclusions

To avoid parameter bias due to model misspecification, non-saturated models should be avoided when the full model approach with predefined relations is used.

These results show parameter precision advantages of a full random effects model (FREM) compared to a full fixed effects model (FFEM).

Allowing more covariates to enter a model without detriment to parameter precision may be particularly important for a full model approach where necessity to select among contending covariates of interest and with likely influence may lead to model misspecification and/or loss of information.

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