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# Linearization of full random effects modeling (FREM) for time-efficient automatic covariate assessment

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## Background

Full Random Effects Modeling (FREM) is a methodology for covariate modeling whereupon all covariate–parameter effects are estimated simultaneously (through parameter–covariate covariance estimation). It has been used with NONMEM, is implemented in PsN [1] and the technique and motivation has been described before. [2][3][4]

Linearization, also implemented in PsN, allows automatic linearization of an estimated model at the typical population parameters. Only the random effects of the model are then estimated (conditional on the nonlinear typical values). [5] It has been shown to enable fast and relatively unbiased approximations of the nonlinear model where the typical values are not expected to change, such as during covariate modeling. [6] Linearization is utilized by default in the new QA PsN tool to speed up the procedure, of which FREM constitutes an important component. [7]

**Aim:** To explore performance, characteristics and differences of linearized FREM in the context of automatic model assessment, where the full PsN functionality may be run on linearized models.

## Methods

To investigate linearized FREM, 25 in-house NONMEM models with covariate data were subject to FREM estimation with and without linearization through the QA tool (PsN 4.7.13, NONMEM 7.3.0); Many of which were selected for fast nonlinear runtimes. Models were only excluded if linear–nonlinear base model evaluation absolute dOFV>3 (linearization may be imperfect), or the estimation terminated without a final OFV for either final FREM model.

Results were then compared with respect to coefficients, estimation time and OFVs. To compare strength of relation independent of covariate spread, coefficients were standardized by the standard deviation of the covariates. Difference in coefficients (univariate and multivariate), runtimes (identical hardware and software) and correlations of OFVs and coefficients were explored.

## Results

3 models showed dOFV>3 (of -8, -11 and 103) and 2 (nonlinear) FREM models crashed, leaving 20 models with results. 916 coefficients could be calculated from these. Five linearized base models dropped more than 3 in OFV during estimation (coloured red in figures). Final FREM estimation times spanned a large range (0.38s, 8.0h). The mean runtime of linear and nonlinear FREM models were 12s (median: 3.3s) and 31min (median: 1.8min), respectively. On average, linear final FREM models executed (not including the covariance step) 510 times faster.

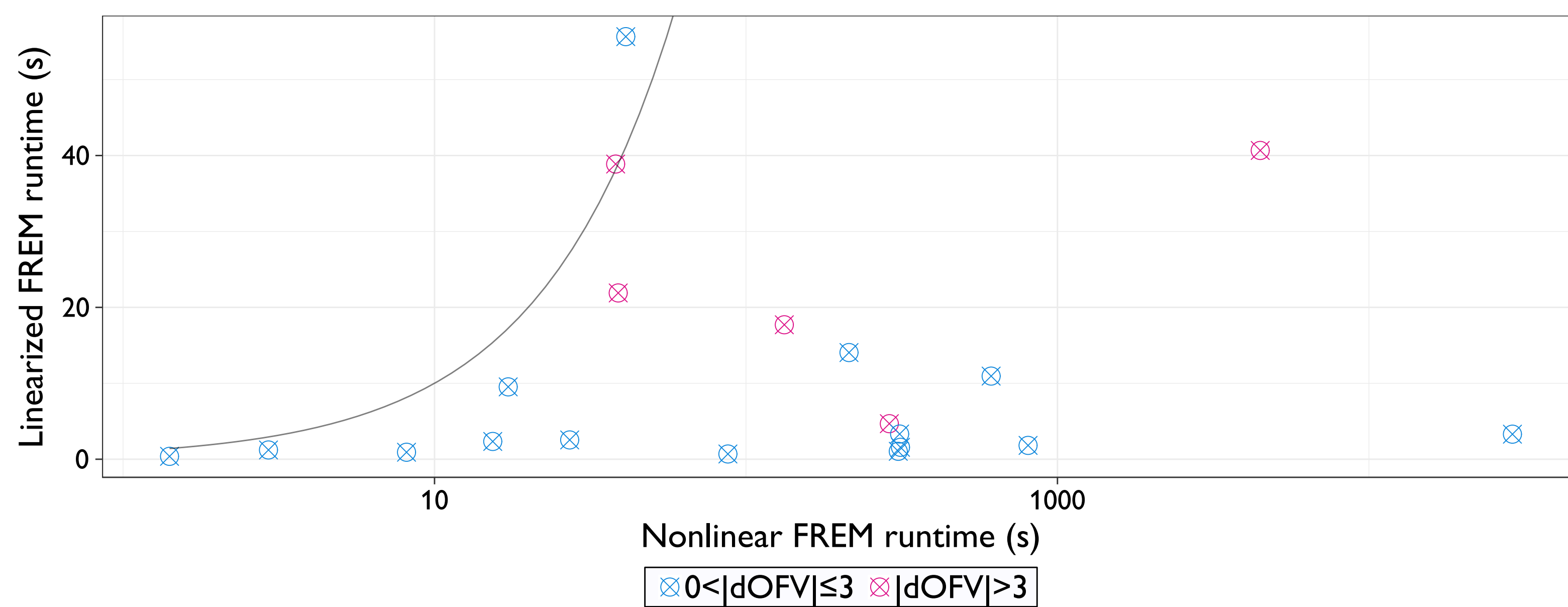


Figure 1: Estimation runtimes for linearized versus nonlinear FREM executions as a semi-log (unit curve drawn) scatterplot. Nonlinear runtimes ( $x$ -axis) are distributed on log scale.

The mean absolute univariate coefficient size was 0.107 and 0.0935 across all linear and nonlinear results, respectively. The mean difference was 0.0418, with no bias discernible. Similarly, multivariate means were 0.141 and 0.140 (mean difference: 0.0488). Only 5/20 FREM models shared a successful covariance step. However, success was more frequent for linear (11) than nonlinear (6) executions.

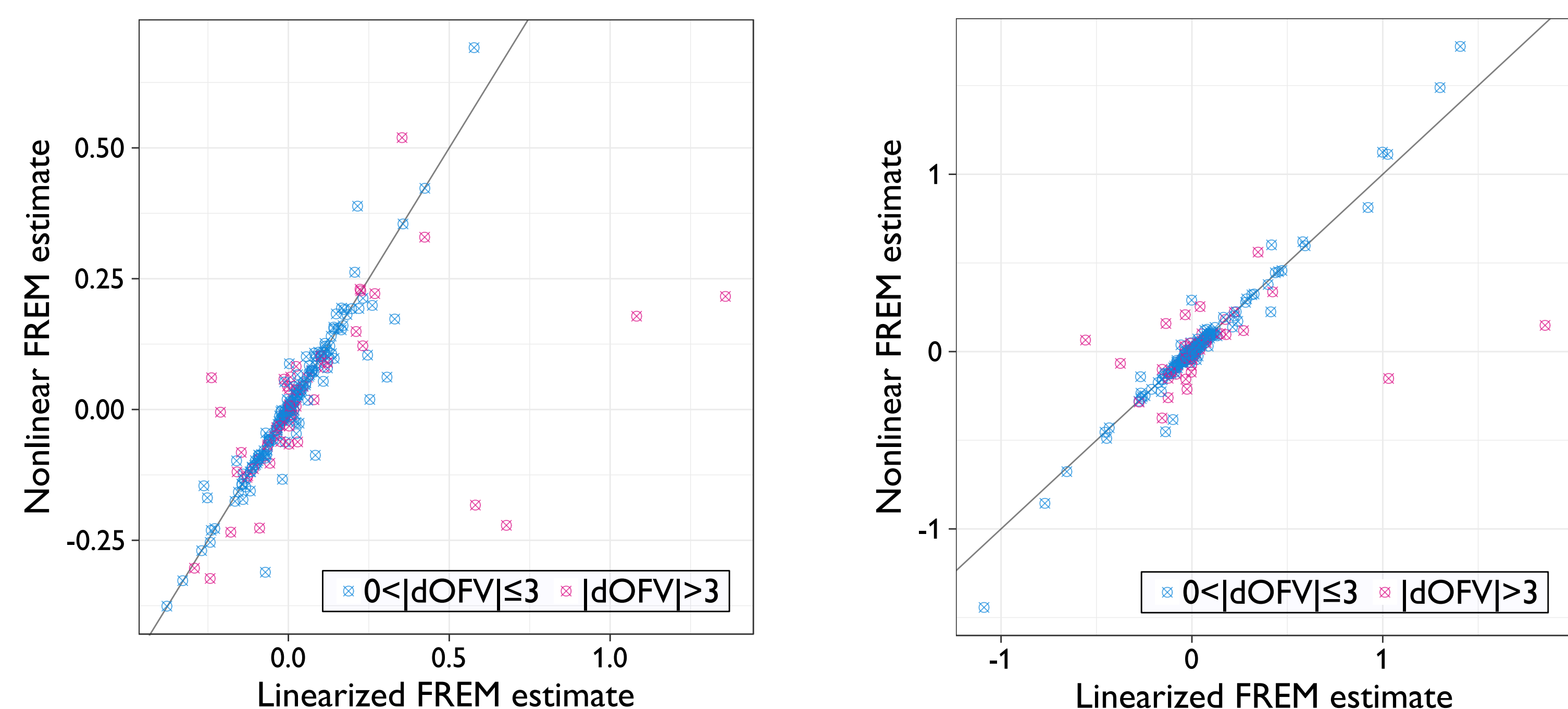


Figure 2: Standardized univariate (left) and multivariate (right) coefficients for all models

Linear–nonlinear correlation coefficients were 68% and 83% for all univariate and multivariate coefficients respectively, and 93% and 98% when excluding the five dOFV>3 models. Digoxin PD correlated the least (37% and 16%) and had a final nonlinear FREM model OFV drop of 0.

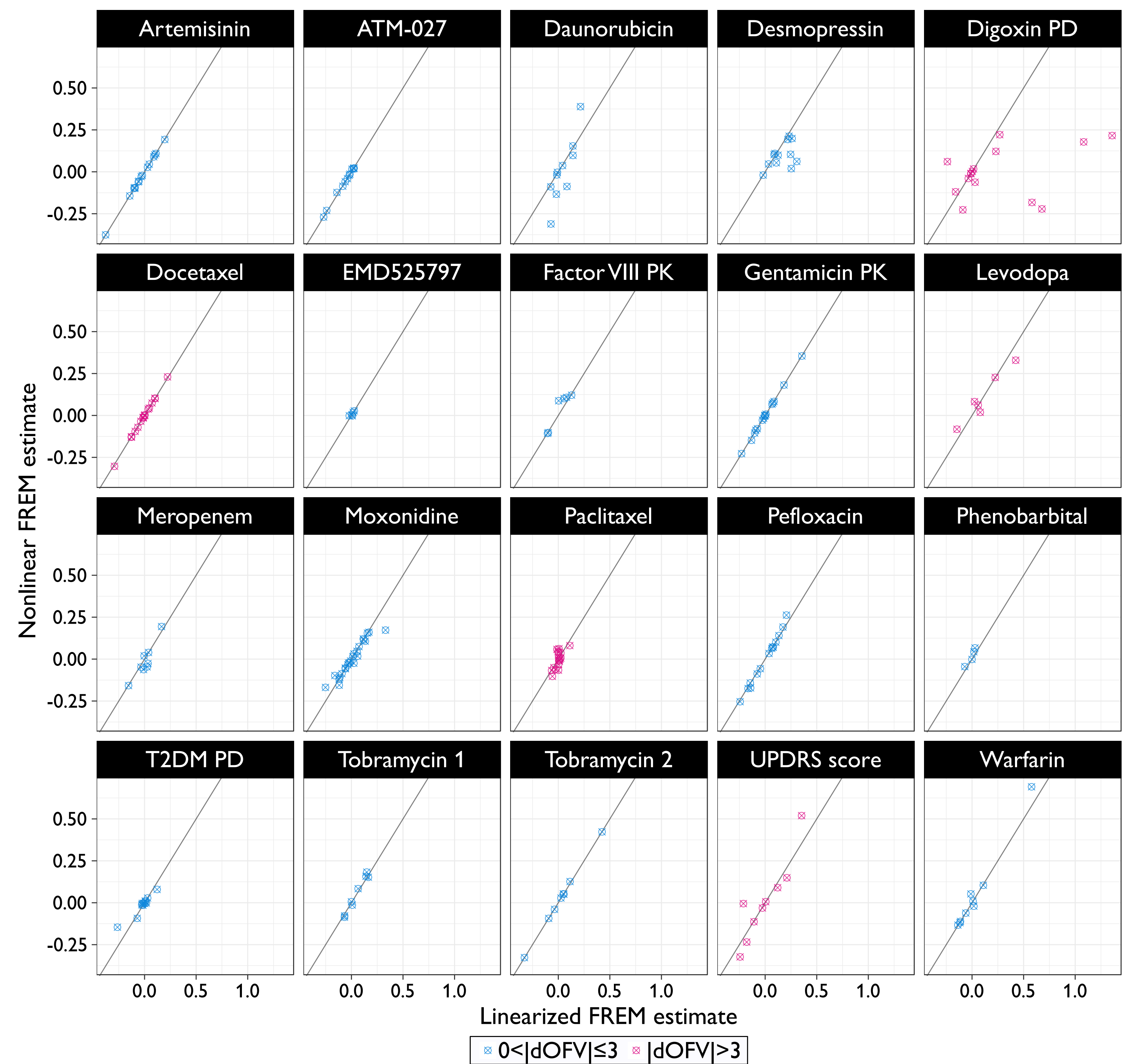


Figure 3: Standardized univariate coefficients for each model separately

OFV drop from full block model including the covariate observations (before joining the matrices and estimating the parameter–covariate covariances) to the final FREM model OFV, may be indicative of "overall importance" of the covariates. Correlation was 96% but only 8.5% amongst the 5 models with dOFV>3 (Digoxin PD deviated the most; linearized drop was 46.5 units lower).

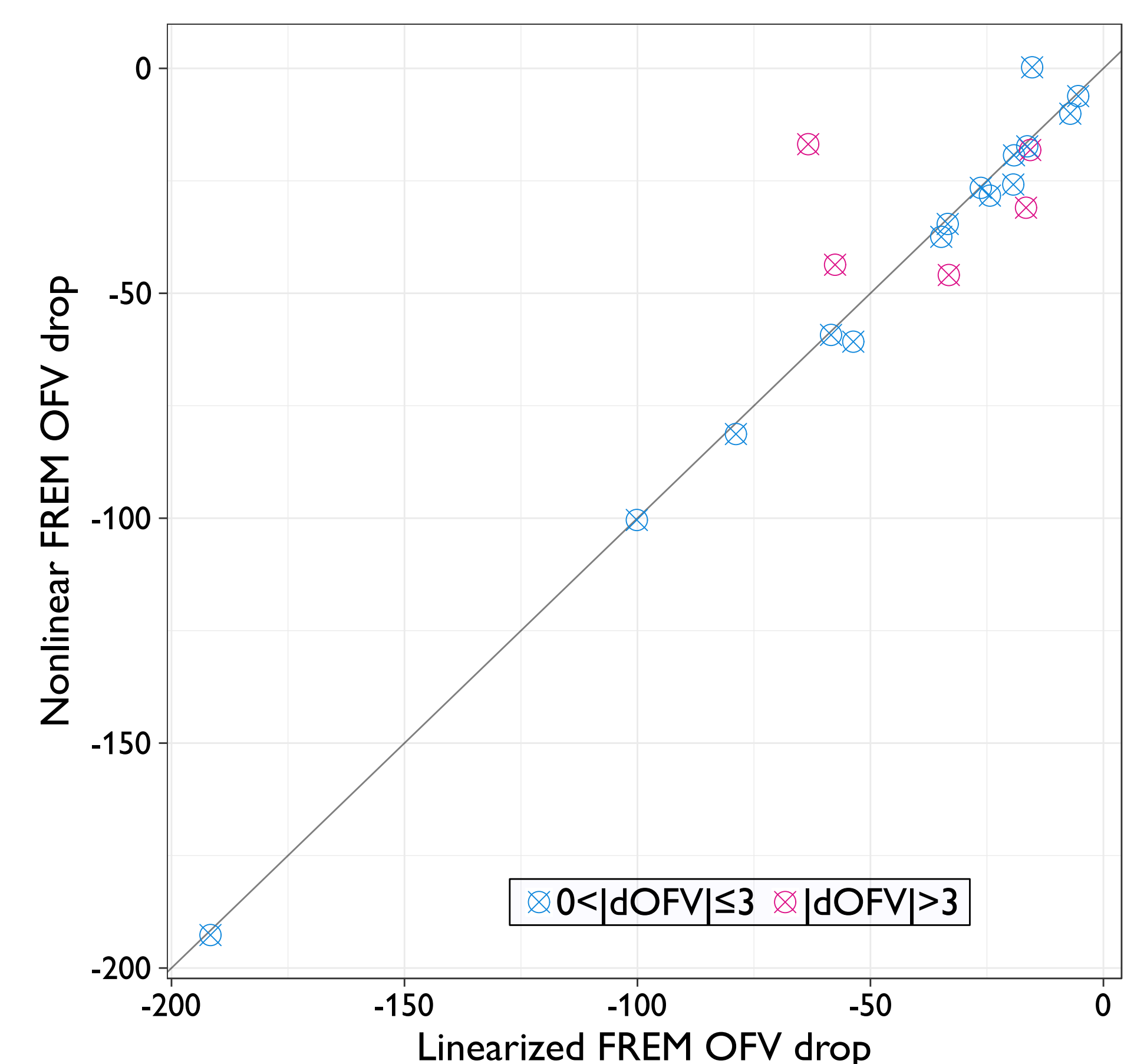


Figure 4: Difference in OFV between full block model with covariate distributions estimated (but without parameter–covariate covariances) and final FREM estimation for linearized and nonlinear executions

## Conclusions

Similar estimates of the coefficients of covariate–parameter relations are obtained when using a nonlinear and linearized implementation of the FREM model. Differences appear not to be systematic, but a higher degree of concordance can be seen when estimated nonlinear and linearized base models show similar OFVs. These results supports linearized FREM for time-efficient estimation of covariate effects in automatic model assessment.

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