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The LASSO – A Novel Method for Predictive Covariate Model Building in Nonlinear Mixed Effects Models

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Introduction - Covariate Selection in Nonlinear Mixed Effects Models

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- Stepwise-Covariate Modelling (SCM)
- Some of the problems with SCM:

1. Border-line significant covariate effects either discarded or included
   - ➢ The LASSO would shrink these covariate effects but may keep them in the model
2. User must specify p-value for selection
   - ➢ The LASSO uses cross-validation
3. Long computer-run-times
   - ➢ The LASSO may be faster

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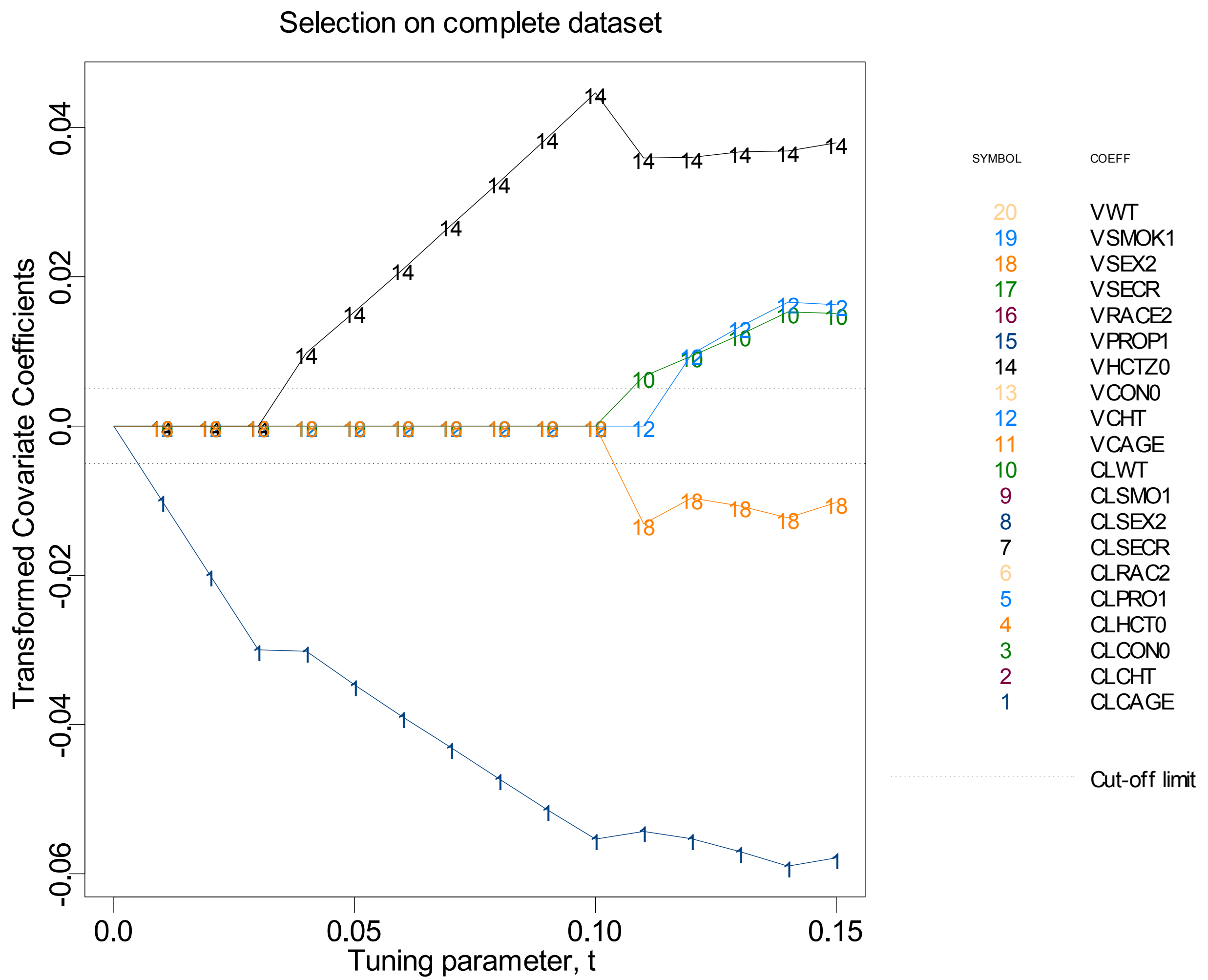
Theory - LASSO for “Least Absolute Shrinkage and Selection Operator”

- Covariate transformation
  - centred around zero
  - normalised to between-individual standard deviation (unless time-varying covariates)
- Covariate-coefficient magnitude on same scale
- Estimating the lasso model:
  - estimating full covariate model with restriction
    - absolute sum of covariate coefficients ≤ t
  - t (tuning parameter), determines Model Size

Theory - Illustration of the LASSO-Estimates over t



Objectives

To implement the LASSO for covariate selection within NONMEM and to compare this method to the commonly-used SCM

Method – Implementation of the LASSO

- Implemented as a fully automated tool using Perl-speaks-NONMEM (PsN)

- Optimal t estimated using cross-validation
  - Cross validation similar to data splitting but uses data more efficiently
  - Five-fold cross validation on NONMEM objective function value (OFV)

Method – Creation of Analysis Datasets

- Analysis datasets generated by sampling subjects (with replacement) from a PK dataset containing 721 subjects
  - 40, 60, 120 or 180 subjects in each analysis dataset
  - 100 replicate dataset of each size

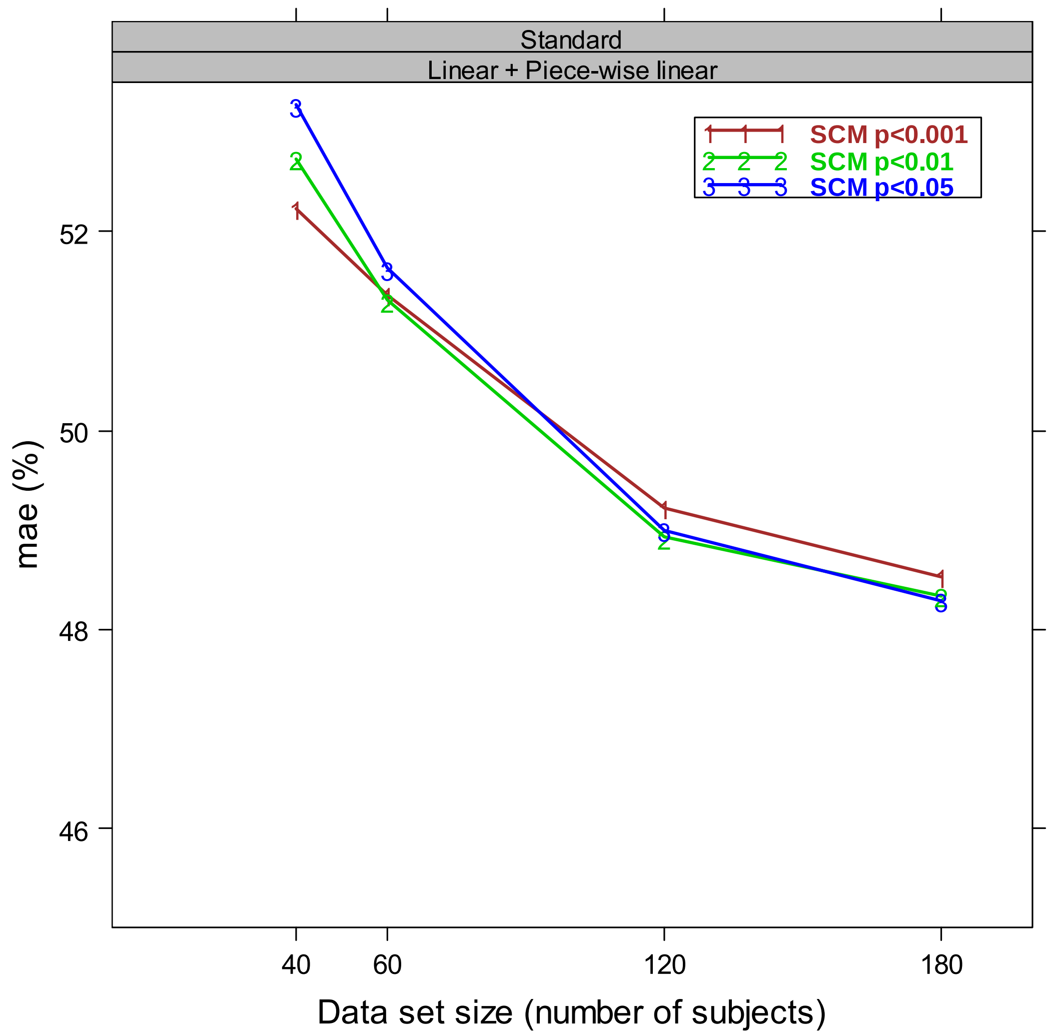
Method – Creation of Validation Datasets

- For each analysis dataset a validation dataset was created comprising all subjects among the 721 that were not in the corresponding analysis dataset

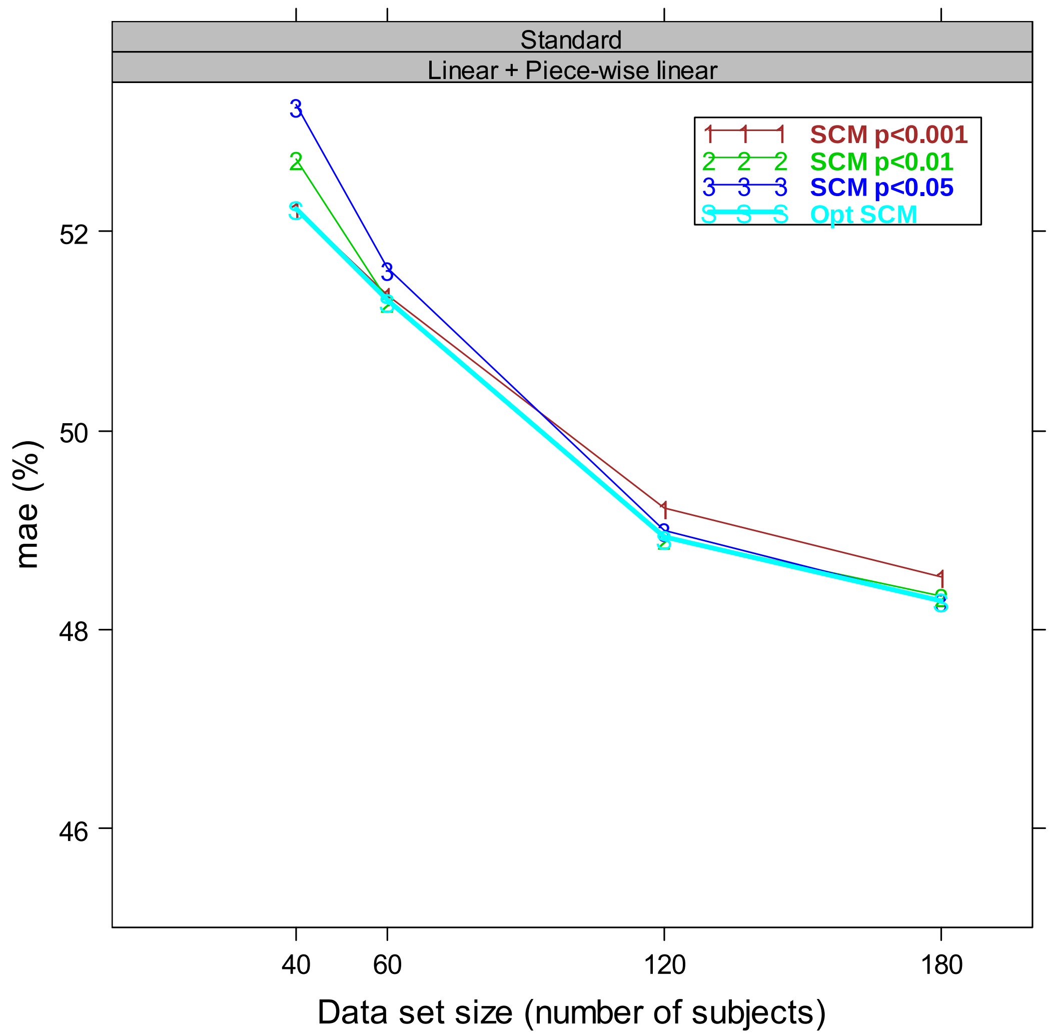
- To compare models produced by SCM and LASSO, prediction error evaluated on observations in validation dataset:

    - mae = average($|obs_n - pred_n| / obs_n$)$\cdot$100%

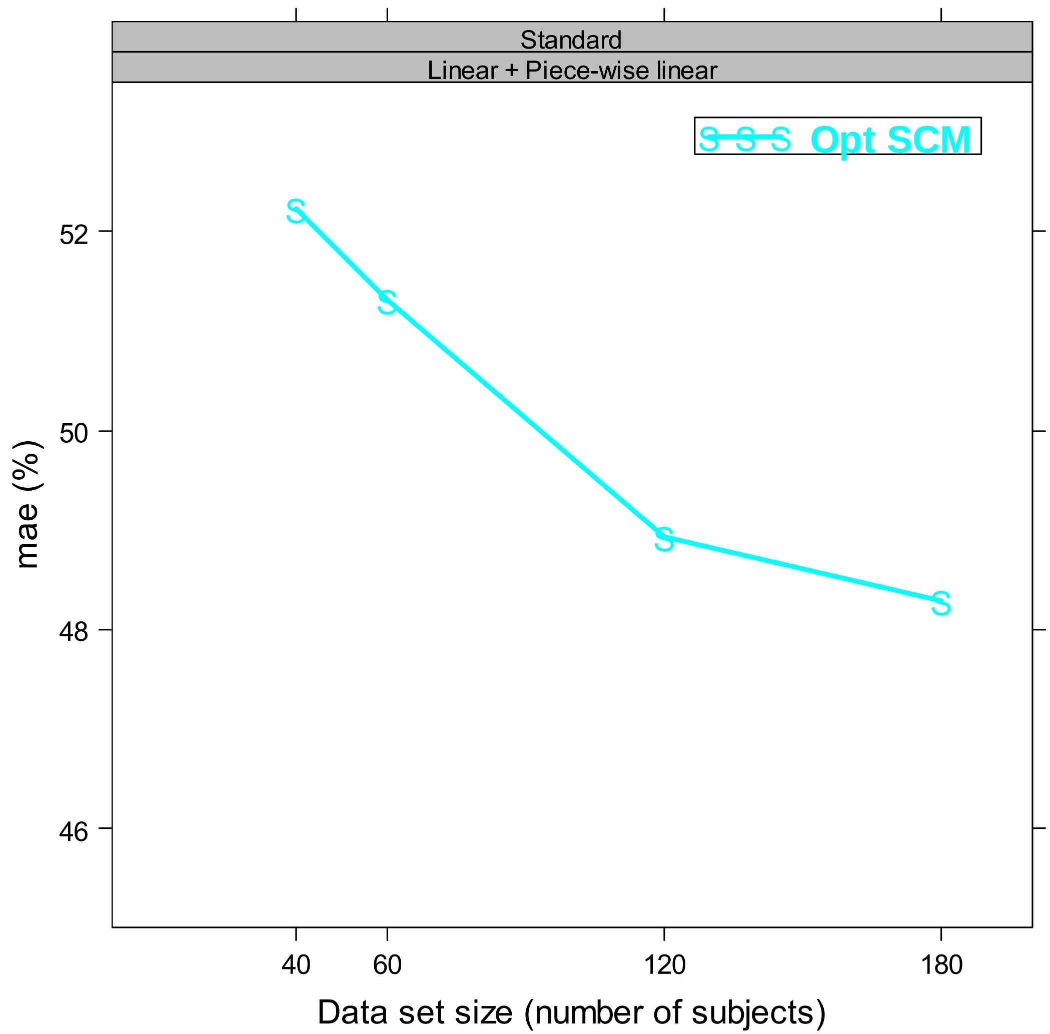
Results – Prediction Error for the SCM with Different p-values



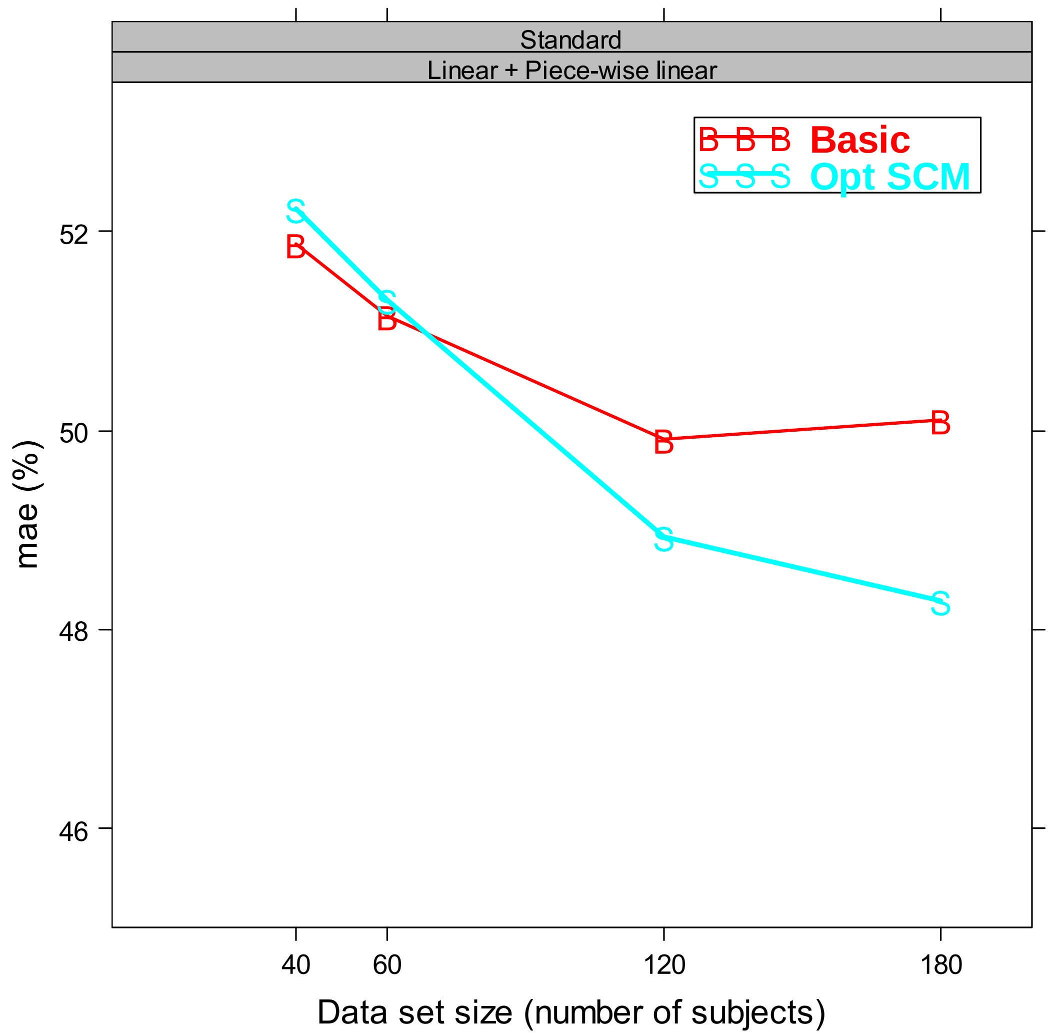
Results – Prediction Error for the SCM with Different P-Values



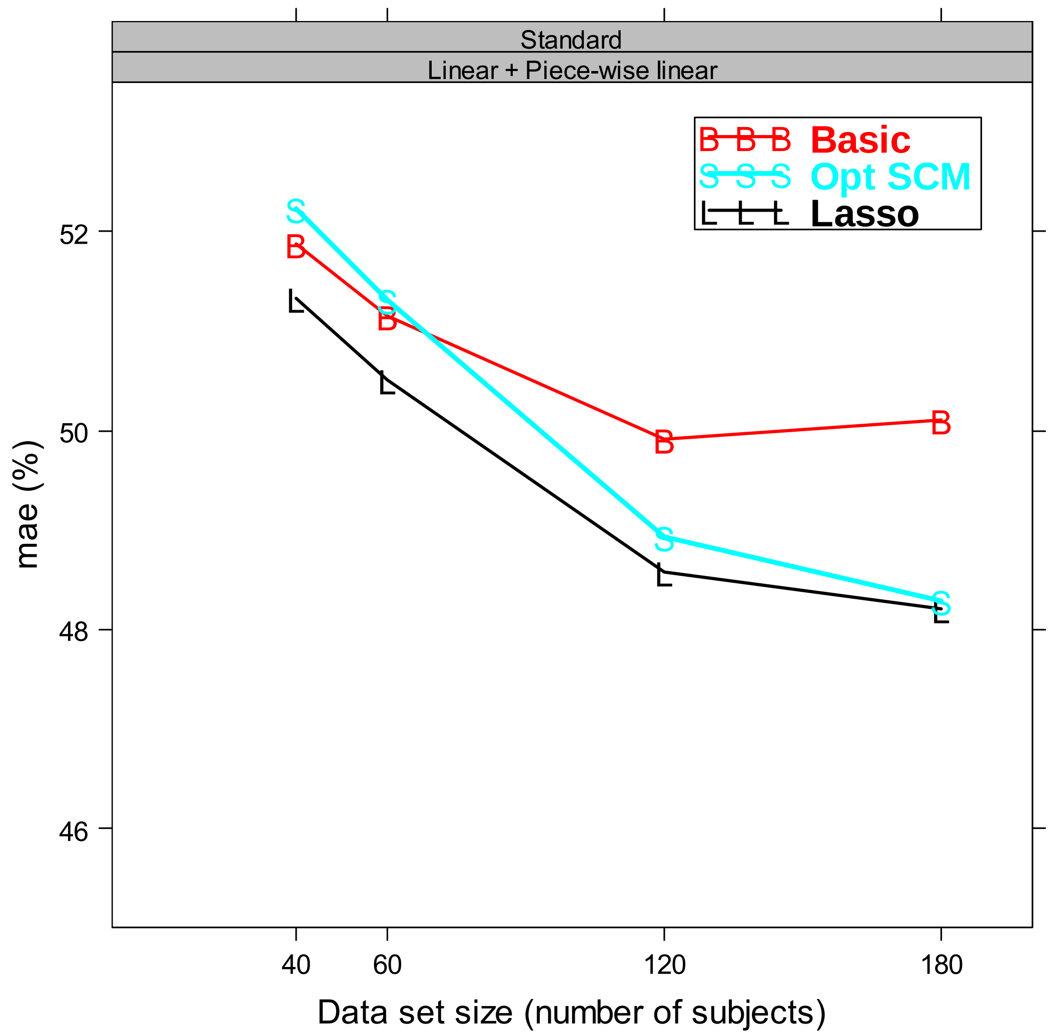
Results – Prediction Error for SCM



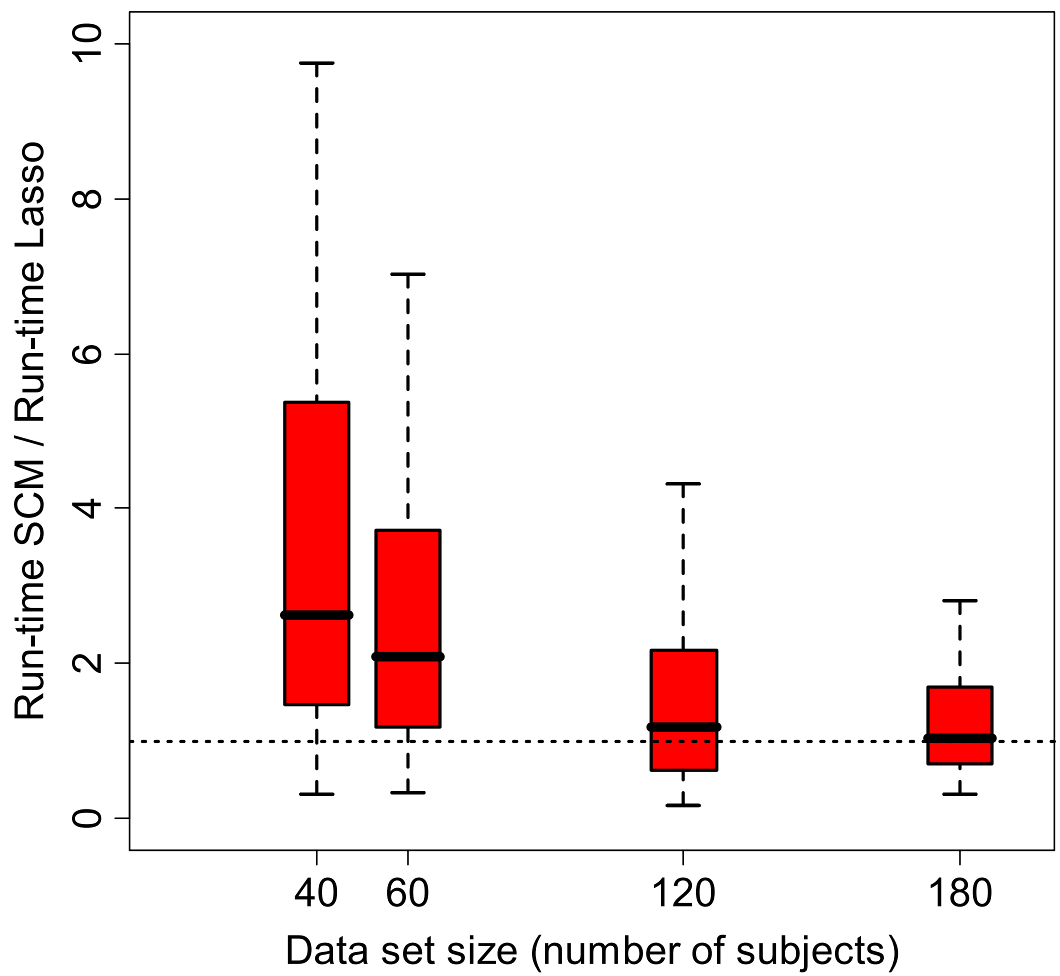
Results – Prediction Error for SCM and Starting Model



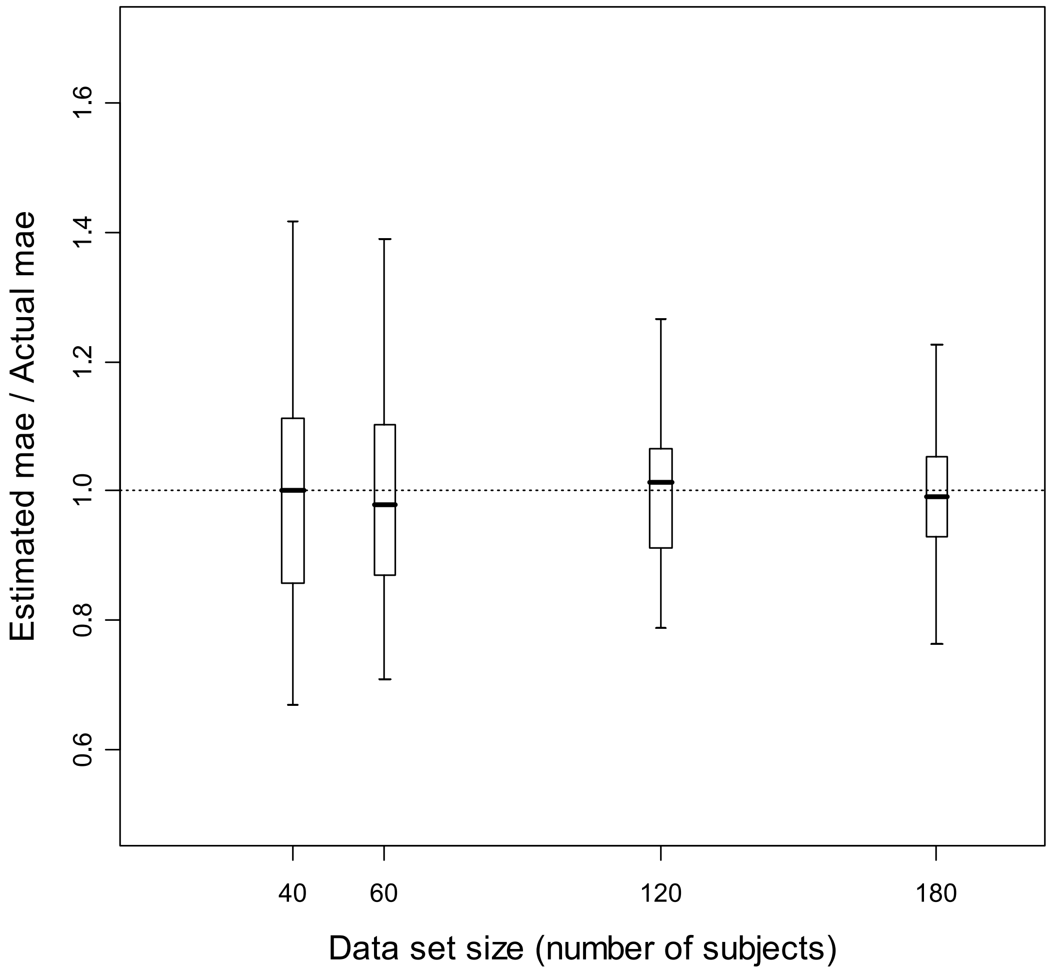
Results – Prediction Error for SCM, LASSO & Starting Model



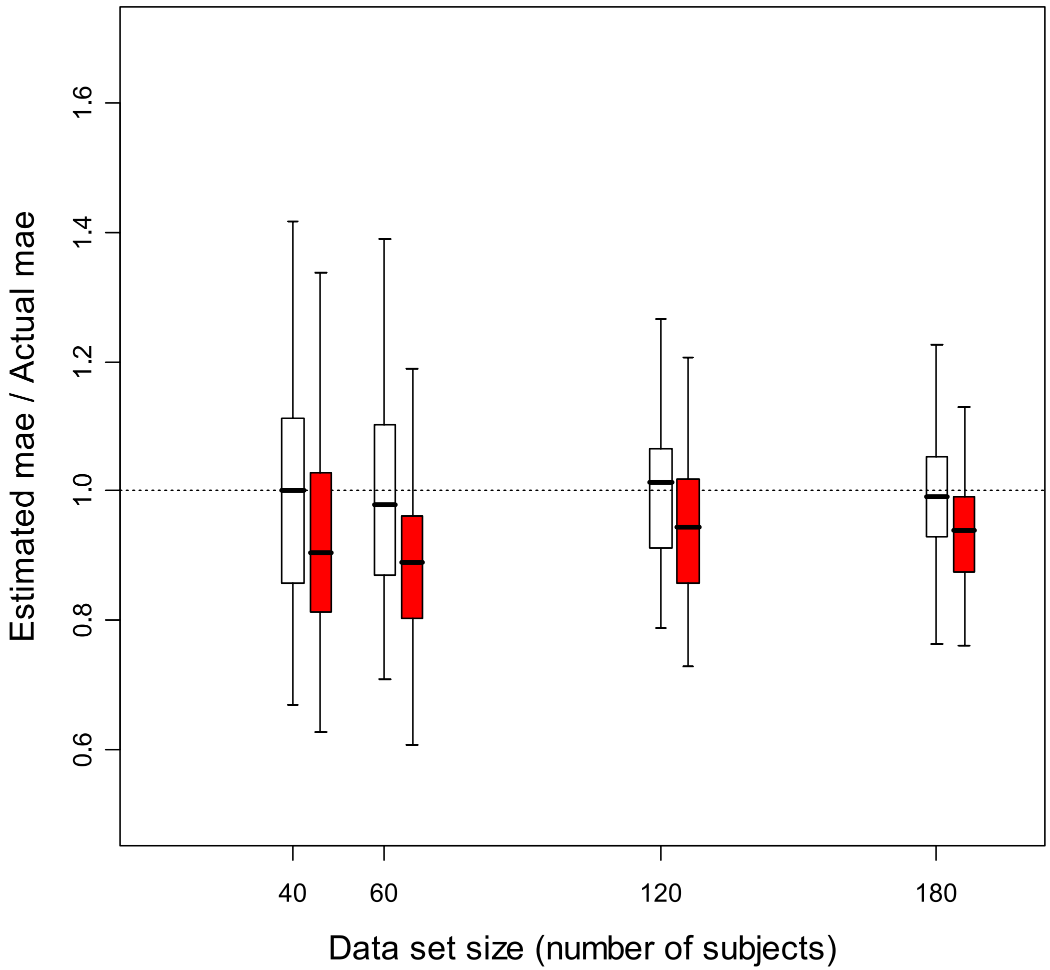
Results – Computer Run-Time



Results – LASSO Provides Unbiased Estimate of Prediction Error



Results – SCM Provides No Accurate Estimate of Prediction Error



Discussion and Conclusions – Drawbacks of the LASSO

- May produce a more complex model
- Cross-validation difficult on unstable model
  - Estimable on 80% of the original data
- Little experience of this method in pop PK/PD

Discussion and Conclusions – Advantages of the LASSO

The LASSO is preferable for small datasets

- Better predictive performance
  - Also for small subpopulations in large datasets!
- Shorter run-time if many covariate relations

- No need to specify a p-value for selection

- Provides estimate of prediction error
  - Covariate-model selection taken into account
  - External validation of covariate model!

Take-Home Message

On small datasets use the LASSO rather than the SCM

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Acknowledgements

- AstraZeneca and Per-Henrik Zingmark
  - Data
- Lars Lindbom and Pontus Pihlgren
  - Cluster and PsN
- Mats Karlsson and Nicholas Holford
  - Valuable discussion and suggestions