

Objective

- **Aim:** To propose and implement a new version of Lasso, called Adjusted Adaptive Lasso (AALasso) [1], for covariate model building in non-linear mixed effects models when multicollinearity exists among covariates.
- AALasso was compared to the Adaptive Lasso (ALasso) [2] and simple Lasso [3] in terms of mean absolute prediction error (mae) and error of estimated coefficient of first covariate.

Methods

AALasso: This new method takes into account the ratio of the standard error of the maximum likelihood estimator, $s_{k(\hat{\beta}_{ML})}$, to the maximum likelihood coefficients, $\hat{\beta}_{k(ML)}$, as initial weight in Lasso to deal with multicollinearity. Thus, we define the weights $\hat{w}_k = \frac{s_{k(\hat{\beta}_{ML})}}{|\hat{\beta}_{k(ML)}|}$. AALasso estimates can be solved by the following algorithm [4].

Algorithm :

- Find $\hat{w}_k$
- Define $x_k^{**} = x_k / \hat{w}_k$, where x_k is the value of covariate k.
- Solve the Lasso for all t values using Lasso tool in PsN,

$$\hat{\beta}^{**} = \arg \min \left\{ \sum_{i=1}^N \sum_{j=1}^n (C_{obs,ij} - \hat{C}_{ij}^{**})^2 \right\} \text{ subject to } \sum_{k=1}^{N_{cov}} |\beta_k| \leq t$$

Where $\hat{C}_{ij}^{**}$ is predicted according to x_k^{**} and t is a tuning parameter which selects the model size and is estimated by cross validation. N, n and N_{cov} are number of subjects, number of observations per subject and total number of covariates, respectively.

- Output $\hat{\beta}_{k(AALasso)} = \hat{\beta}_k^{**} / \hat{w}_k$

ALasso estimates are computed similar to AALasso using the algorithm except that the initial weights are defined as $\hat{w}_k = \frac{1}{|\hat{\beta}_{k,Lasso}|}$.

Simulation study: data sets were simulated from one compartment i.v bolus model using the following values and constituted 16 scenarios:

- Number of subjects : 20, 40, 80, 120
- Number of observations per subject: 3 observations at time points of 0.1, 2, 3.5
- Number of covariates: 10
- Vector of the true coefficients: $\beta = (0.25, 0.15, 0.1, 0.05, 0, \dots, 0)$
- Correlation among covariates: 0, 0.2, 0.5, 0.7

The natural logarithm of typical value of clearance was a linear function of covariates which were created by sampling from a multivariate normal distribution with the above value of correlations among them.

All scenarios were replicated 100 times. Training data were generated for every simulation scenario and each replication and it was used for model fitting. A large data including 5000 individuals and three observation per individual were generated as validation data for every simulation scenario. In order to evaluate the performance of Lasso, ALasso and AALasso, we computed mean absolute prediction error (mae) for the three methods and also True model which was reestimated, on the validation data sets, using MAXEVALS=0. Moreover, error on estimated coefficient of first covariate was computed in all scenarios.

Software: SSE and Lasso tools in PsN were applied to simulate and estimates all models, respectively. The statistical software RStudio 0.98 using R 3.1.2 and ggplot2 2.1.0 were implemented to generate statistical analysis and graphical presentation.

Results

- The AALasso had better predictive performance compared to ALasso and Lasso when number of subjects is low. However, when the correlation among covariates increased the difference of mae between AALasso and the other two methods decreased, Figure 1.
- Increasing correlation among covariates resulted in increasing mae of all methods, including the True model. The mae of all methods approached the mae of the True model when the number of subjects rose, Figure 1.
- The AALasso had a lower error on the estimated coefficient of the first covariate than ALasso and Lasso, except in two scenarios in which the variability for ALasso is much higher than for AALasso, Figure 2.

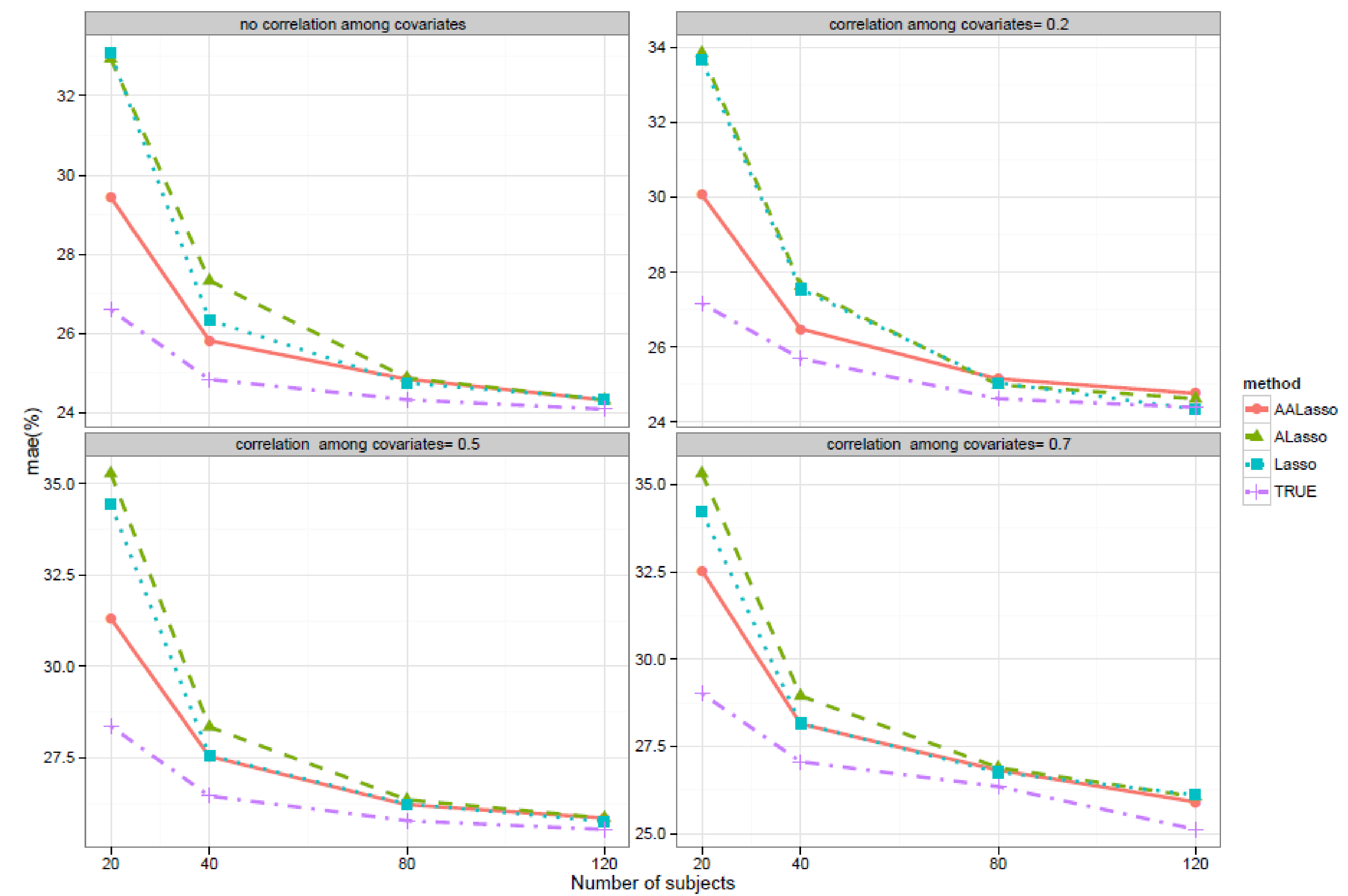


Figure 1. Mean absolute prediction error (mae) for AALasso, ALasso, Lasso and TRUE model in 16 scenarios were all combinations of four different number of subjects(x-axis) and different value of correlation among covariates.

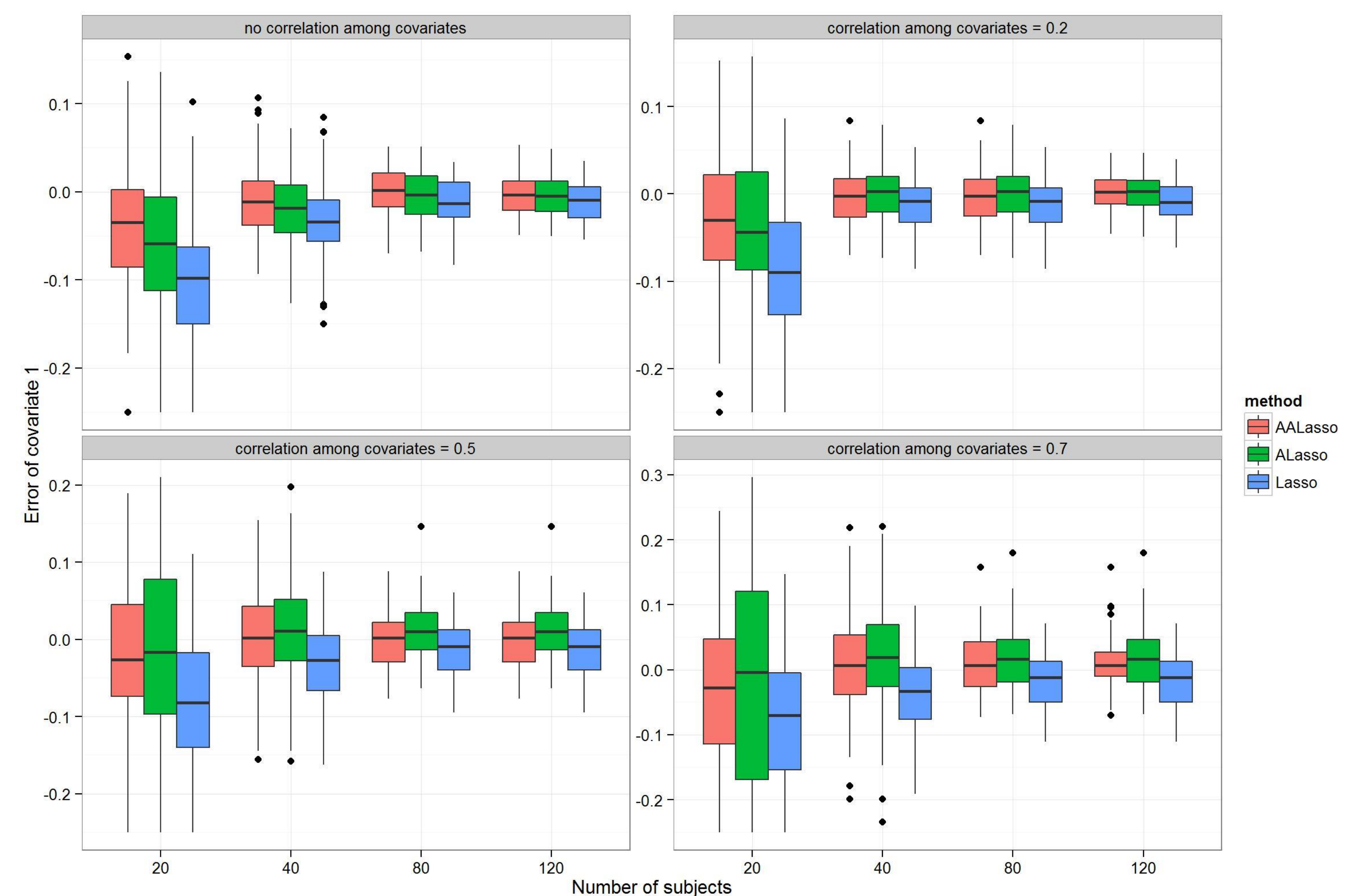


Figure 2. Box plots of error on estimated coefficient of first covariate for AALasso, Alasso and Lasso in 16 scenarios.

Conclusions

- AALasso identifies influential covariates with good predictive performance for small data sets.
- AALasso performs well even in small data sets in which high multicollinearity exists among covariates.

References

- [1] Qian W, Yang Y. Model selection via standard error adjusted adaptive lasso. Annals of the Institute of Statistical Mathematics. 2013;65(2):295-318.
- [2] Zou H. The adaptive lasso and its oracle properties. Journal of the American Statistical Association (2006), 101:1418–1429.
- [3] Ribbing J, Nyberg J, Caster O & Jonsson E.N. The lasso-a novel method for predictive covariate model building in nonlinear mixed effects models. J Pharmacokin Pharmacodyn (2007). 34 (4):485–517 .
- [4] Algamal Z. Y & Lee M. H . Adjusted adaptive lasso in high-dimensional poisson regression model. Modern Applied Science (2015), 9(4):170–177.