Influence of Covariance Step Success on Final Parameter Estimates

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Objective and Hypothesis

To determine if a successful covariance step in NONMEM increases the chance of reaching maximum likelihood, and to investigate the influence of computational stability on final parameter estimates.

Assuming no computational error, the positive-definiteness of the R-matrix (the Hessian of the OFV) is a necessary condition for the maximum likelihood. Therefore we hypothesize that covariance step success should be a necessary condition for the maximum likelihood.

Introduction

The influence of covariance step completion on the quality of parameter estimates in NONMEM has long been debated. Holford *et al* have shown, for a number of examples, that there is no significant difference in parameter standard errors for different termination statuses in a bootstrap [1].

The work presented here assesses different levels of computational stability and different initial estimates for a model without altering the model, data, or the OFV at maximum likelihood.

Method

Three PK models were examined ten thousand times each using FOCEI estimation in NONMEM 7.3:

1. Two-compartment model with simulated data
2. One compartment Phenobarbital example model and data included in NONMEM [2]
3. Model by Jönsson *et al* [3] with original data

Computational stability and initial estimates were altered between estimations. To change computational stability the models were linearly reparametrized using the precond [4] script in PsN, to produce an R matrix at ML with condition number between 1 and 10^{15}.

The initial values of the model parameters were randomly perturbed within an order of magnitude around the best estimate in order to investigate initial estimates far from ML.

The result of each estimation was categorized into one of four groups:

1. Minimization successful and covariance step successful
2. Minimization successful, but failed covariance step
3. Failed minimization, but successful covariance step
4. Failed minimization and failed covariance step

Results: Local Convergence

The variation in initial estimates and computational stability exposed several local convergence OFVs. In Figure 1 we can see the ML OFV and several clear local convergence OFVs as horizontal lines.

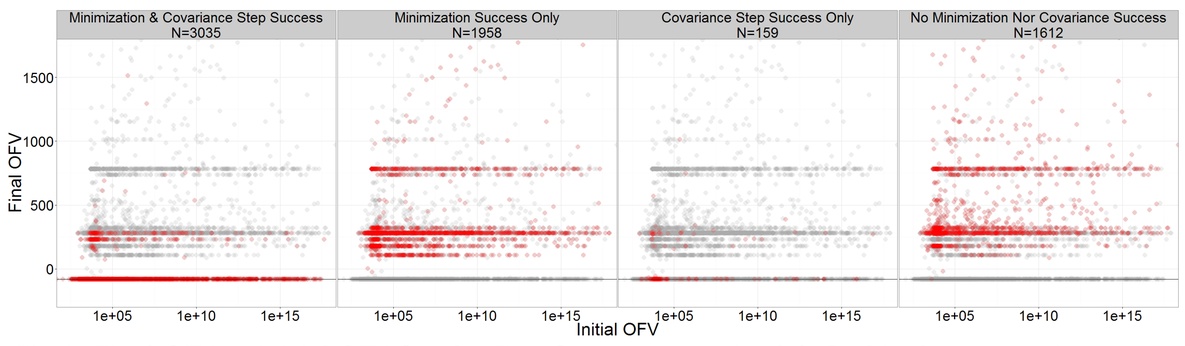

Fig 1. Final OFV vs Initial OFV for the Two Compartment Model. Red is the respective group highlighted against the grey background of the full data.

Conclusions

Covariance step success appears to be a better indication of parameter estimate quality than minimization success.

Estimated parameters are most unlikely to be at ML if the covariance step fails and the initial values were not already close to ML.

Our next step is to expand our exploration to different estimation methods and a wider range of models.

Results: Successful and Unsuccessful Estimations

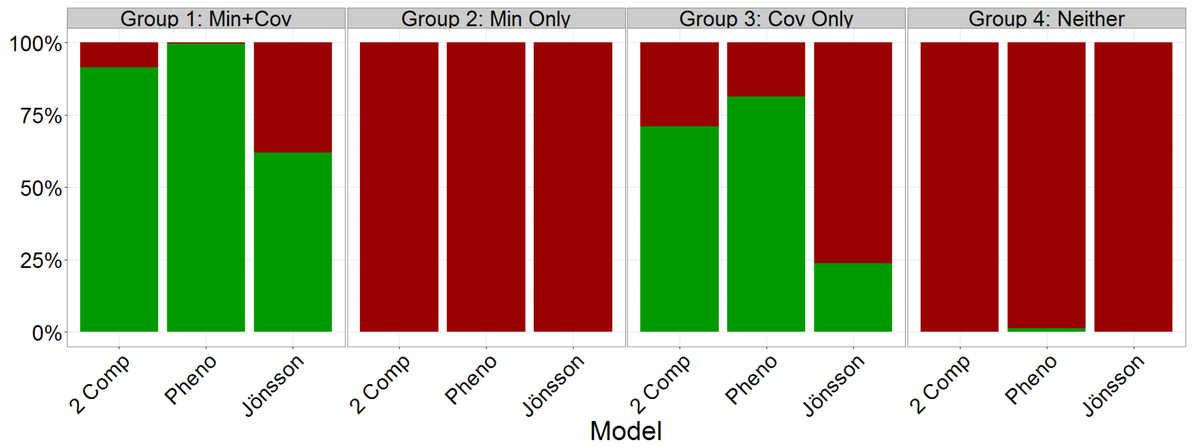

Fig 2. Percentage of runs that have reached minimum OFV (green) split by group and model. Minimum OFV was accepted as less than the total minimum OFV for that model plus one.

The final OFVs for runs with both minimization and covariance step successful were overwhelmingly reaching the maximum likelihood estimate, although some differences between models could be observed. In Figure 2 we can see the proportions between estimations with acceptable OFV values in green (OFV <= minimum OFV + 1) and estimations that produced a higher OFV in red.

Group 1 consists largely of runs that reach maximum likelihood, while groups 2 and 4 are almost void of successful estimation.

Figure 3 explores the relationship between computational stability and the final OFV for the Phenobarbital model.

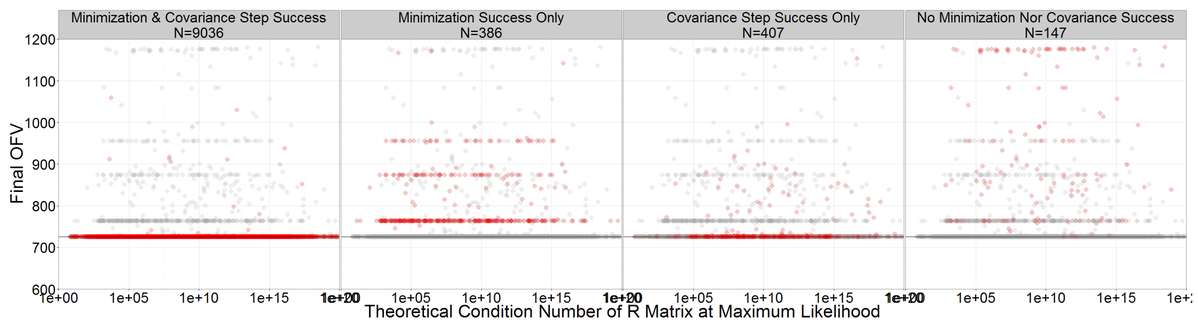

Fig 3. Final OFV vs the Optimal Condition Number of the R Matrix. The Phenobarbital model is stable but the pattern with group 2 and 4 failing to reach minimum OFV

The published model by Jönsson *et al* follows the same pattern as the two other included models, but is slightly less stable in this experiment setup as demonstrated by its lower rate of success in Figure 2. In Figure 4 we can see the final OFV versus initial OFV for the Jönsson model.

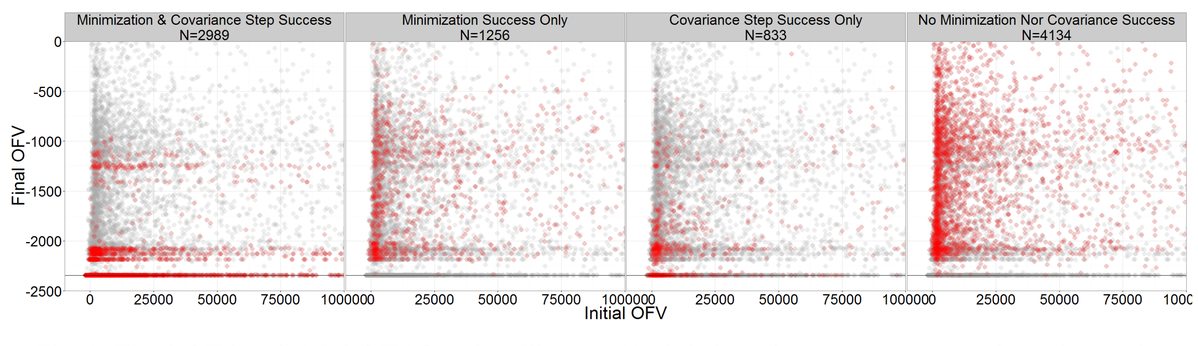

Fig 4. Final OFV vs Initial OFV for the Jönsson Model. Local convergence and a minuscule portion of runs reaching maximum likelihood in groups 2 and 4 is evident.

References

[1] Holford N *et al*, NONMEM Termination Status is Not an Important Indicator of the Quality of Bootstrap Parameter Estimates, PAGE 15 (2006) Abstr 992 [www.page-meeting.org/?abstract=992]

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[3] Jönsson *et al*, Population pharmacokinetic modelling and estimation of dosing strategy for NXY-059, a nitrone being developed for stroke, Clinical Pharmakocinetics (2005), 44(8):863-78

[4] Aoki *et al*, Preconditioning of Nonlinear Mixed Effect model for Stabilisation of Covariance Matrix Computation, PAGE 24 (2015) Abstr 3586 [www.page-meeting.org/default.asp?abstract=3586]

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