Linear approximation methods for fast evaluation of random effects models

Elin M Svensson, Mats O Karlsson
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Objective

The objective of this work was to develop and assess a fast method for evaluation of IIV, IOV and residual variability (RV) model components.

Methods

The linear approximation (Eq. 2) of a nonlinear model (Eq.1) was based on a previously published first-order conditional estimates linearization [1]. Derivatives from a basic nonlinear model were used in the extended linear models.

$$y_{ij} = f(\vec{p}_i, \vec{x}_{ij}) + h_{ij} \qquad \text{Eq. 1}$$

$$y_{ij} \approx f(\vec{p}_i, \vec{x}_{ij})|_{Q_0} + \sum_{l=1}^{m} \frac{\partial f}{\partial \eta_{li}}|_{Q_0} (\eta^*_{li} - \hat{\eta}_{li}) + \sum_{v=1}^{\tau} \left(\frac{\partial h_{ij}}{\partial \varepsilon_{ijv}}|_{Q_0} + \sum_{l=1}^{m} \frac{\partial}{\partial \eta_{li}} \left(\frac{\partial h_{ij}}{\partial \varepsilon_{ijv}}|_{Q_0} \right)|_{Q_0} (\eta^*_{li} - \hat{\eta}_{li}) \right) \varepsilon^*_{ijv} \qquad \text{Eq. 2}$$

Where $Q_0 = \{\vec{\hat{\varepsilon}}_{ij} = \vec{0},\ \vec{\eta}_i = \vec{\hat{\eta}}_i\}$, m is the number of elements in $\vec{\eta}_i$ and τ is the number of element in $\vec{\hat{\varepsilon}}_{ij}$.

Three earlier described, real data analyses (data1: moxonidine [2], data 2: pefolxacine [3] and data 3: ethambutol [4]) were used to compare the results from nonlinear models with the corresponding linear version.

The results were assessed based on the difference in objective function value (ΔOFV) between a basic model and extended models for the nonlinear and linear estimation methods respectively. The RV models evaluated were extensions to an additive, a proportional or a combined additive and proportional error model and included:

- IIV on the RV
- autocorrelation
- a power model (Eq. 3)
- time dependence (Eq. 4)

$$h_{ij} = IPRED^{\theta} \cdot \varepsilon \qquad \text{Eq. 3}$$

$$h_{ij} = \varepsilon$$
$$IF(TAD \leq break\ point\ time)\ h_{ij} = \theta \cdot \varepsilon \qquad \text{Eq. 4}$$

IIV and IOV variances and covariances, not estimated in the basic model, were added in the extended models. The analysis was carried out in NONMEM 7.2 [5] aided by PsN [6].

Results and Discussion

The nonlinear and linear approaches gave the same results for models with additive RV. For models with proportional RV the individual ETA estimates sometimes got caught in local minimas which caused deviating results. Modelling the data on logarithmic scale and hence transforming the RV to additive solved the problem. For models with a combined RV a strategy including a dynamic scedasticity and transform-both-sides model [7] proved successful.

The ΔOFV from the linear and the conventional nonlinear models agreed well for all the evaluated RV models (Fig. 1a). For IIV and IOV evaluation the ΔOFV agreed well in the lower range but for large ΔOFV and when inclusion of variability resulted in a large change of typical values of the parameters some discrepancies were seen (Fig. 1b-1c). The agreement was acceptable also for IIV and IOV correlations (Fig. 1d).

The linear analysis identified the same extended models to be significant improvements as the conventional nonlinear analysis except in two cases with correlation extensions where ΔOFV was very close to the significance level.

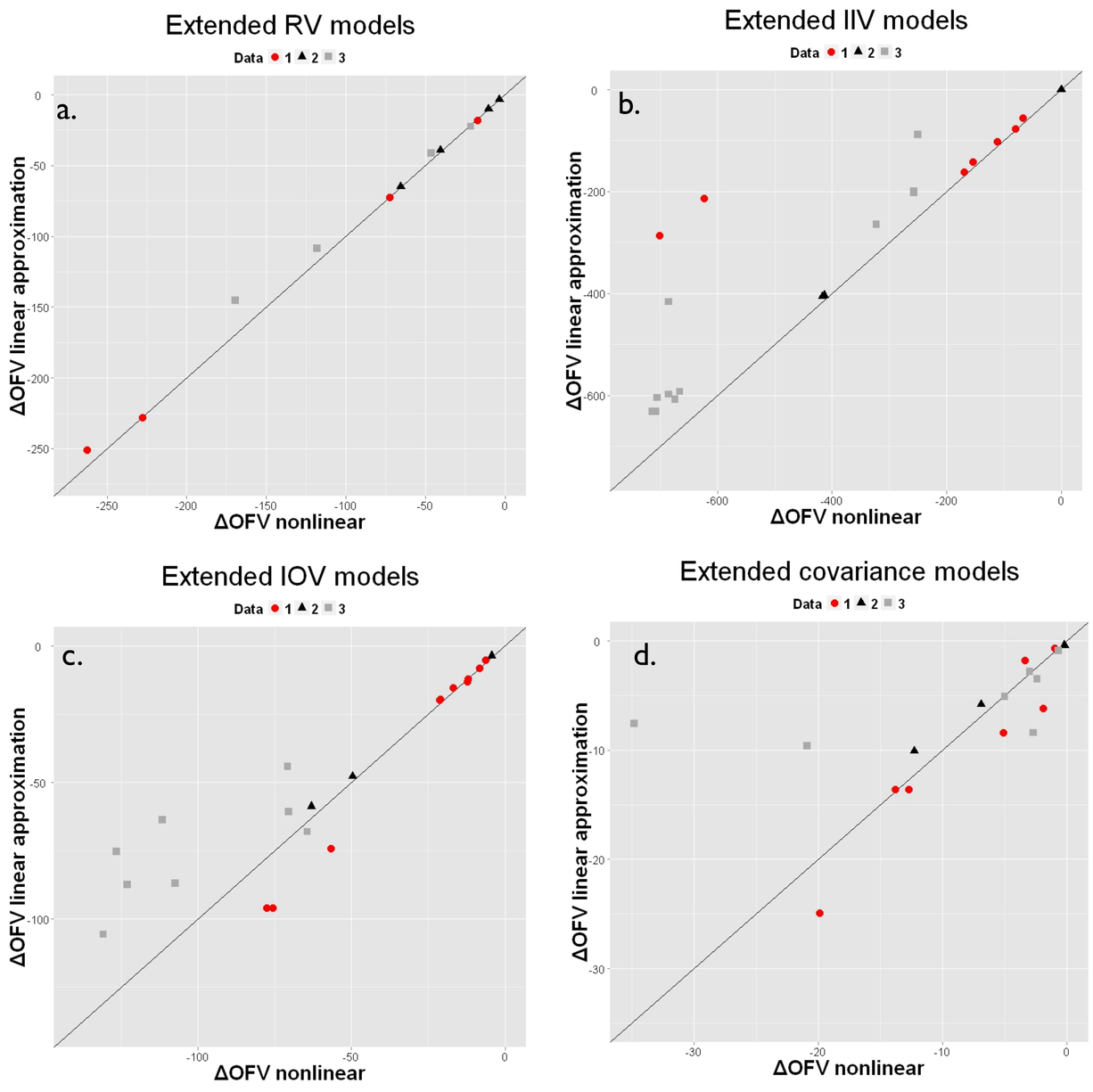

Fig. 1: Difference in OFV between basic and extended model after estimation for nonlinear vs. linear approximation for extended RV (a), IIV (b), IOV (c) and covariance (d.) models.

The total runtime for estimating the four extended RV models for data 3 was 2.4 hours and 3.7 minutes for the nonlinear and linear models respectively. Applying the method to another more complex analysis decreased the time for estimation of a model including a full IIV block of dimension 11 from 26.7 hours to 6.2 minutes.

Conclusions

The linear approximation substantially decreases runtimes and has successfully been used for evaluation of a broad range of random effects models. When the basic RV were not additive the estimation of the linear approximation worked less well but this was circumvented by transformations. The method can be implemented in PsN to further automate and speed up the model development process.

References

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Acknowledgement: The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also supported by financial contribution from Academic and SME partners. This work does not necessarily represent the view of all DDMoRe partners.