Investigation of performances of FOCE and LAPLACE algorithms in NONMEM VI in population parameters estimation of PK and PD continuous data

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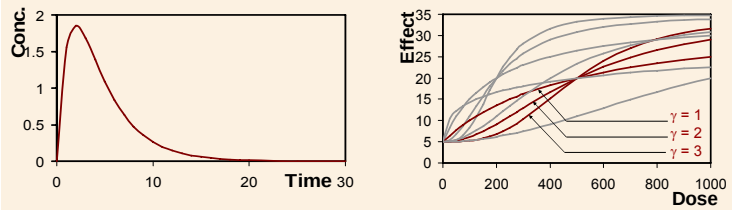
Background and Objective

- At PAGE 2005, a comparison was made by P. Girard and F. Mentré of the performance of several estimation methods used in nonlinear mixed effects modeling [1]. This resulted in only 49% of successful minimisations with FOCE algorithm in NONMEM VIβ. We wanted to investigate the behaviour of NONMEM VI for the same problem.
- In NONMEM VI, a new estimation method, LAPLACE INTER, is now available. While LAPLACE previously have been used mainly for categorical type data, the INTERACTION option is clearly aimed for analysis with continuous type data.
  - **The aim was to compare the estimation performances of different methods in NONMEM VI, with focus on FOCE and LAPLACE methods for continuous data.**

Materials and Methods

- The 100 pharmacokinetic data sets primarily simulated by Girard *et al.* were re-examined using NONMEM VI and NONMEM VI compiled without the warnings, with the methods FOCE, LAPLACE, SLOW, INTER and NUMERICAL.
  - A one-compartment (V) model, with a first order absorption (Ka) and a first order elimination (Ke) was used [Figure 1]. A random effect was multiplicatively affected to each of the three parameters and integrated in a full covariance matrix. An exponential error was also included.
- For further investigations, the difference in performance between the FOCE and the LAPLACE methods was addressed in pharmacodynamic data also, i.e. 100 data sets were generated in NONMEM VI.
  - A sigmoid Hill (γ) model, with a baseline (E_0) and with a correlation between the maximal effect (E_{max}) and the dose needed to obtain half of the maximal effect (ED_{50}), was used to simulate and estimate the data.
  - The model was completed by either an additional residual error or a proportional one inferring an interaction.
  - The effect was measured at four doses (0, 100, 300 and 1000), following different scenarios corresponding to changes made on the initial value of ED_{50}, the Hill factor or the correlation between E_{max} and ED_{50} [Figure 1].



$$C = \frac{D \times Ka}{V \times (Ka - Ke)} \times \left(e^{(-Ke \times t)} - e^{(-Ka \times t)}\right) \qquad E = E_0 + E_{max} \times \frac{D^{\gamma}}{D^{\gamma} + ED_{50}{}^{\gamma}}$$

Figure 1. *Data that were analyzed were simulated from a 1-compartment PK model and a hill factor PD model with different scenarios.*

Results

- As regards to the PK data,
  - 100% successful minimisations were obtained with NONMEM VI both with and without warnings, and between 33% and 63% successful covariance steps. Otherwise, overall results were similar to those obtained in NONMEM VIβ by P. Girard *et al.* and similar between the different methods.
- Regarding PD data estimations,
  - Minimizations properties were poorer concerning LAPLACE than FOCE [Table 1].

Table 1. *Successful minimizations.*

(%)	Hill = 1	Hill = 2	Hill =3
FOCE	100	100	80
LAPLACE	100	66	43
F INTER	100	97	92
L INTER	98	73	61

  - Small variations in bias (= mean(Est–True)/True×100), and precision (root mean square error RMSE = $\sqrt{(\text{mean}(\text{Est}-\text{True})^2/\text{True}^2)}\times 100$) were observed when changing other parameters initial values, whereas increasing the Hill factor led to an augmentation of the difference between estimates and true values.
  - For the model without interaction, a trend of improvement both on bias and RMSE was seen in estimations with LAPLACE compared to FOCE [Figure 2], although high gradients were sometimes recorded with LAPLACE; while they were similar, except for the highest Hill factor, for the model including an interaction.

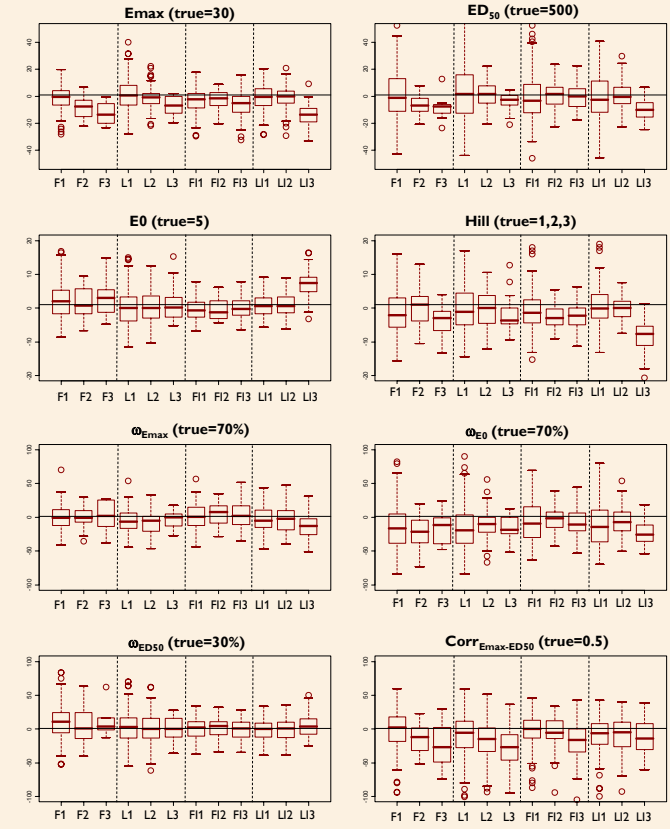


Figure 2. *Boxplots of relative estimation error RER(%) = (Est–True)/True×100 obtained on estimations of E_{max}, Hill, ED_{50}, E_0, ω_{Emax}, ω_{E0}, ω_{ED50} and correlation E_{max}-ED_{50}, for 6 simulations scenarios with γ = 1, 2, 3 and ε additive or proportional. Methods used were: FOCE (F), LAPLACE (L), FOCE INTER (FI) and LAPLACE INTER (LI).*

Discussion and Conclusion

- For PK data, minimisations were 100% successful with FOCE in NONMEM VI. For PD data, successful minimisations were considerably more likely with FOCE than LAPLACE. There was no apparent difference however, in estimates from successful and not successful fits.
- LAPLACE (INTER) seems to be more accurate but less robust than FOCE (INTER), as recently indicated through single data set analysis [2].

References

[1] P. Girard and F. Mentré. A comparison of estimation methods in nonlinear mixed effects models using a blind analysis. PAGE 14, Pamplona, Spain.
[2] R.J. Bauer, S. Guzy, and C. Ng. A survey of population analysis methods and software for complex pharmacokinetic and pharmacodynamic models with examples. The AAPS journal. 9:E60-83 (2007).