DEVELOPMENT OF A SIMULATION TOOL TO SIMULATE INTRA -INDIVIDUAL VARIABILITY ENCOUNTERED IN ANIMALS FROM STANDARD PRECLINICAL TOXICOLOGICAL STUDY

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INTRODUCTION - OBJECTIVE

The aim of this work was to develop a tool enabling us to simulate concentrations in S-PLUS according to:

- a user-defined study design used in preclinical toxicology studies
- a compartmental pharmacokinetic model with known population parameters and inter (IIV) and intra individual variability (IAV).

The rational was to explore Nonmem fitness of purpose regarding parameter estimations in the context of a preclinical toxicological study with sparse sampling strategy.
Autocorrelation is often high between 2 close successive sampling times in the same animal taking part in a toxicological study, because animals belong to the same standard population. In order to develop a simulation tool to simulate IAV, we decided to compare two IAV models. Two scripts were written in S-plus®[1] to simulate these 2 models. Script 1 is a proportional error model whereas the 2nd script is the same error integrating an autoregressive model of order 1 (Rho). Both methods were used to simulate datasets.

We will present the results of different simulations according to each method and the results of estimations in Nonmem®[2].

MATERIAL AND METHOD

Concentrations were simulated according to a mono-compartmental intravenous bolus model with linear elimination and single dose administration.

In script 1, individual concentrations are calculated with individual clearance and volume, Cl_i and V_i simulated as $Cl_i=CL_{pop}.exp(Eta1)$ with Eta1 normally distributed with mean 0 and user defined variance ω_i with $CV = \sqrt{\omega_i}$. The individual concentration is :

$$c_{ij} = \frac{D_0}{V_i} \cdot e^{-\frac{Cl_i}{V_i} \cdot t_{ij}}$$

For the i^{th} individual at time j. The final concentration with error model is $C_{ij} = c_{ij} \cdot (1 + Err(1))$
Err(1) is normally distributed with mean 0 and user defined variance ω_i with $CV = \sqrt{\omega_i}$

The script 2 simulates Cl_i and V_i similarly to script 1, the error model includes an autocorrelation. The autocorrelation may be fixed between 0 for no correlation to 0.99 extremely correlated. 13 values of Rho were investigated.

$$cor(\varepsilon_t, \varepsilon_s) = \rho^{|t-s|}$$

Covariance between observations for the same animal decreases toward zero with increasing time interval between two successive time t and s[3].

The toxicological study simulated was a matrix of rats as detailed below. This matrix was simulated for 3 doses, 15, 50 and 150 mg and 2 sexes. The total number of rats per simulation was 54.

TIME	RAT 1	RAT 2	RAT 3	RAT 4	RAT 5	RAT 6	RAT 7	RAT 8	RAT 9
0.05	X	X	X				X	X	X
0.25									
0.5	X	X	X						
1				X	X	X			
3	X	X	X						
4				X	X	X			
8				X	X	X			
10							X	X	X
24							X	X	X

Compound X parameters were used as population values, Clpop and Vpop were set at 0.021 L/h and 0.975 L respectively. Their inter-individual variability (IIV) was fixed to 20 %. The intra-individual variability (IAV) was fixed to 15 %.

The percentage prediction error was calculate as $PE(\%) = \frac{\theta_i - \theta_i^*}{\theta_i^*}.100$ with θ_i estimated value and θ_i^* theoretical value.
Mean and standard deviation of PE% were used as measure of accuracy and precision.

For each Rho, 100 simulations were performed. Estimations were made using Nonmem® version V, subroutine ADVAN1 TRANS2 and algorithm FO, FOCE, FOCEI. First we did not correct for the autocorrelation in the Nonmem control file. Then autocorrelation was taken into account by adding the modified verbatim code used by Karlsson *et al*.[4]

RESULTS AND DISCUSSION

Using Rho allows to smooth the concentration-time profile. The effect of rho on concentrations is shown below.

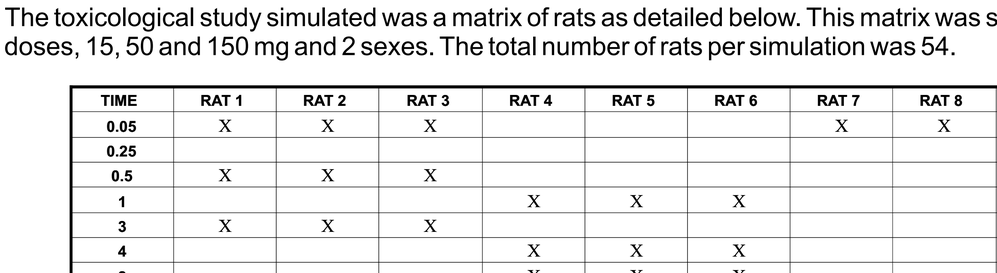

Figure 1 Two concentration profiles simulated with 3 different values of Rho

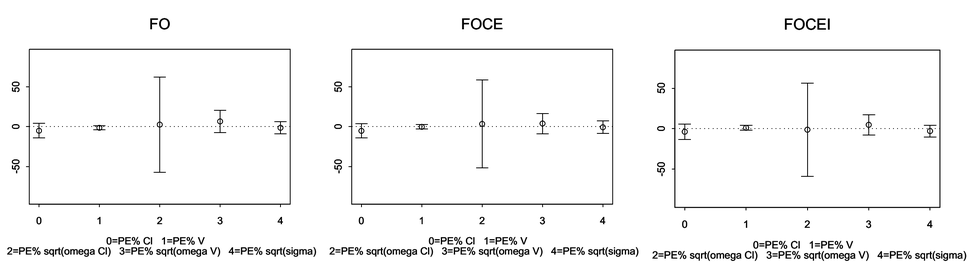

Figure 2 Script 1 results for FO FOCE and FOCEI, o mean, ± standard deviation

Script 1 results are similar to script 2 results when Rho is low whatever the algorithm.

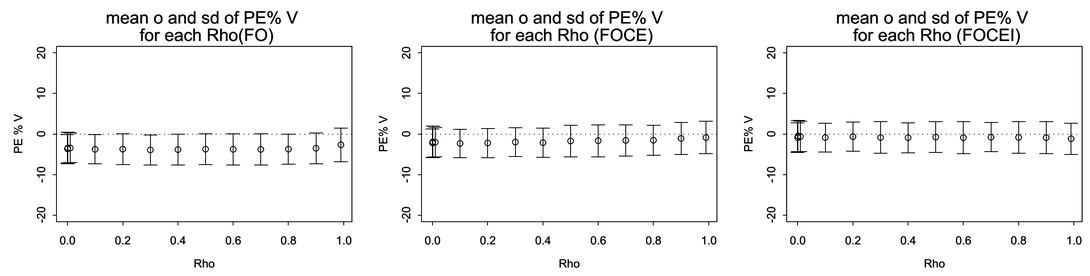

Figure 3: Estimation of population parameters is not changed with the value in Rho, the estimation is better with FOCEI compared to FOCE and FO. Similar results are observed for Clearance. Clearance values are also better estimated with FOCEI.

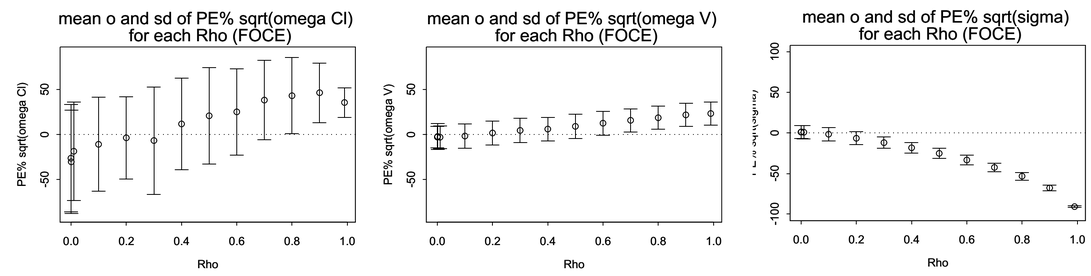

Figure 4: IIV on Cl and V increase with the increase in Rho, whereas IAV decreases. The same trend is observed with each estimation method when autocorrelation is not taken into account. Figure 5 below explores how this can be explained.

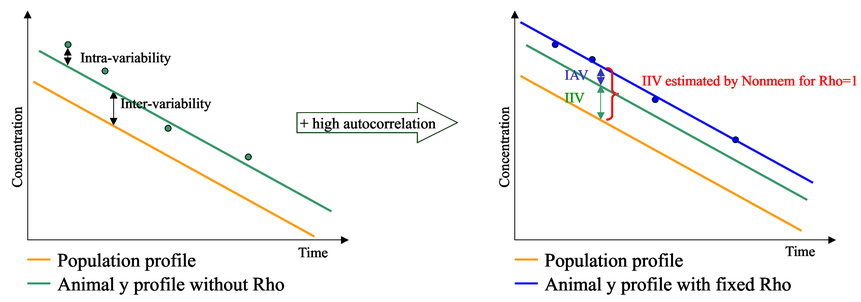

Figure 5 inter and intra variability without (left) and with Rho (right)

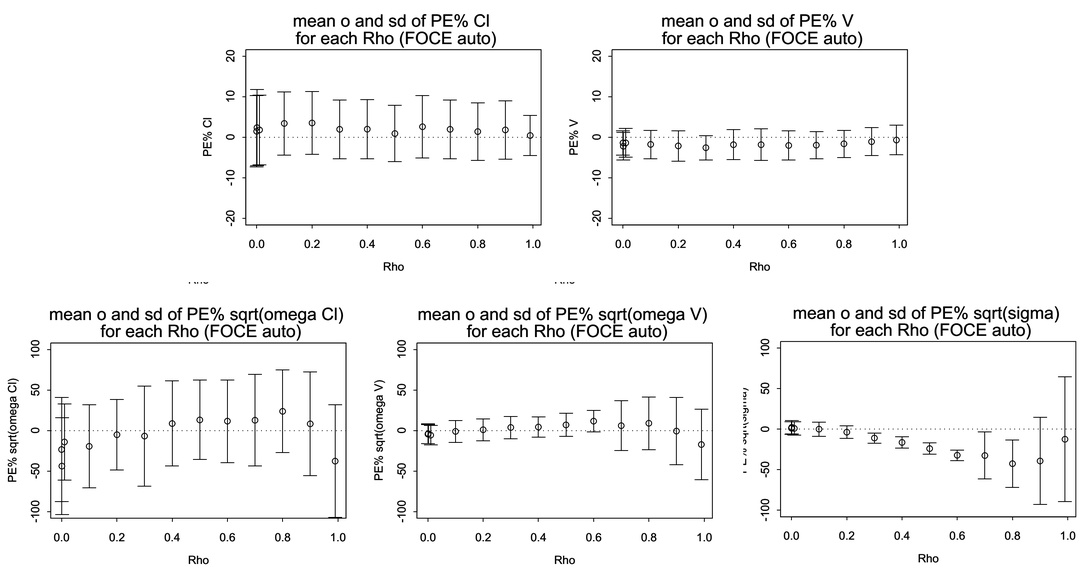

Figure 6: When we introduce the verbatim code in Nonmem® parameters estimations are not affected but both IIV and IAV are. Nonmem® estimates an autocorrelation for Rho equal or superior to 0.8. Above 0.8, IIV and IAV estimations are closer to the values we have used to simulate the concentrations.

CONCLUSIONS

Despite the sparse sampling design used in the toxicological study, population parameters are very well estimated (using Nonmem®) with an accuracy usually less than 15 % whatever IAV, i.e. the value of Rho had little influence on the estimation of population parameters.

Conversely, variability estimations depend upon Rho values. For Rho less than 0.3, estimation of IIV and IAV are good with or without taking the autocorrelation into account. Clearly if the presence of the autocorrelation is ignored in the estimation for Rho values above 0.4, both PE% for IIV of CL and of the IAV especially seem biaised. Adding autocorrelation code in Nonmem improves variability estimation for these values, but an average of 48 runs per rho value for FOCE and 47 for FOCEI aborted.

A rho value lower than 0.4 could reproduce best individual concentrations profiles observed in standard toxicological studies.

Further simulations with different values of variability, IAV models, pharmacokinetic model and study design should take place to study their impact on estimations.

REFERENCES

[1] Insightful (2005) S-Plus version 7.03 users' guide, on-line
[2]Beal SL and Sheiner LB. NONMEM user' guides. San Francisco: NONMEM Project Group, University of California
[3]Littell RC, Pendergast J., Natarajan R. Modelling covariance structure in the analysis of repeated measures data. Stat Med. 2000 Jul 15;19(13):1793-819. Review.
[4] Karlsson MO, Beal SL, Sheiner LB. Three new residual error models for population PK/PD analysis. J Pharmacokinet Biopharm. 1995 Dec;23(6):651-72