Leveraging Two-Stage δ Global Sensitivity Analysis method to inform parameter estimation in PBPK models

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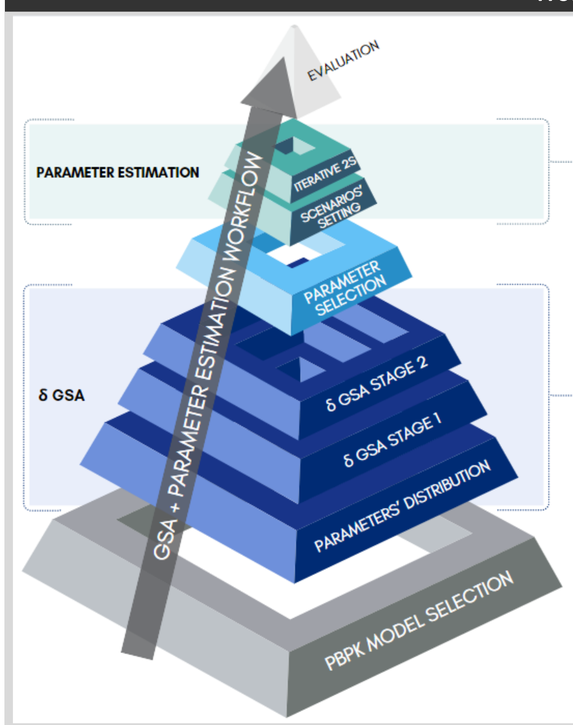
INTRODUCTION AND OBJECTIVES

Therapeutic drug monitoring represents one of the main applications of pharmacometrics in the clinical setting. Parameter estimations are routinely performed for characterizing individual pharmacokinetic (PK) parameters in order to optimize the benefit/risk balance of a patient. In spite of the limitations typically associated with the usage of Physiologically Based Pharmacokinetic (PBPK) models in this area they have demonstrated to be able of coping with limited sampling collection and reliability of predictions specially performing previously a Global Sensibility Analysis (GSA)

In this work, the objectives are : (i) implementing the Two-stage δ Global Sensitivity Analysis method in PhysPK® connected with Python; (ii) assessing the impact of model parameter uncertainties on the main PK endpoints predicted with a PBPK model; (iii) evaluating iterative two-stage (ITS) method for parameter estimation with alternative sampling strategies.

METHODOLOGY AND RESULTS

Workflow strategy



STEP 8 Evaluation of the whole process Estimation performance was evaluated in terms of precision and accuracy

STEP 7 Implementation of the iterative two stage (I2S) I2S estimation method was built and applied for step 7

STEP 6 Scenario setting A set of scenarios was fixed for assessing sampling variations and algorithm robustness

STEP 5 Parameter selection Parameters to estimate were chosen according to a spurious input and physiology principles

STEP 4 GSA stage 2 Step 3 was repeated including correlations between parameters

STEP 3 GSA stage 1 Monte Carlo (MCS) was performed without including correlations between parameters and delta indexes computed to identify parameters impacting on AUC/Tmax/Tmax

STEP 2 Distribution of model parameters Parameter distributions and CVs were accounted

STEP 1 PBPK model and parameter selection Phys-DAT semi mechanistic PBPK model (PhysPK software) was selected [1]

Figure 1. Strategy followed for the development of the Two-stage delta Global Sensitivity Analysis [2] and the parameter estimation. For the moment, only the results until Step 4 have been obtained.

STEP 1 PBPK model and parameter selection

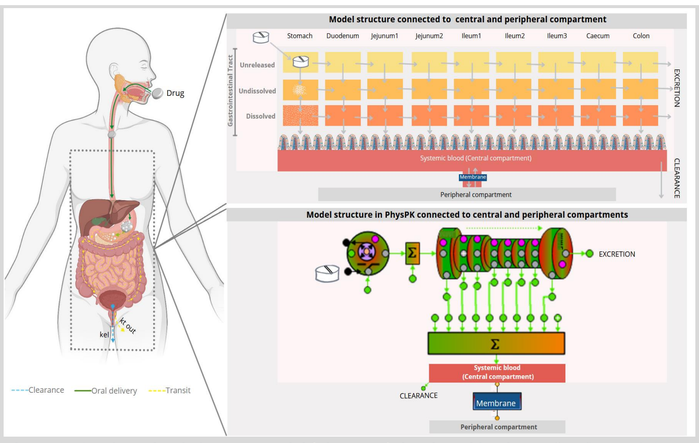


Figure 2. Semi-mechanistic PBPK model (Phys-DAT) developed in PhysPK ® software [1] for orally administered drugs selected for doing the GSA and parameter estimation.

STEP 2 Parameters' distribution

Table 1. Distribution of model parameters selected from the PBPK model considered for the GSA.

Parameters	CV (%)
Stomach pH	3
Stomach volume	10
Stomach emptying rate constant	20
Degree of flatness	10
pH for the rest of the GI tract	3
Volume of the rest of the GI tract	10
Transit of the rest of the GI tract	20
Radius of the rest of the GI tract	10
SAEF of the rest of the GI tract	10
Clearance	
Central volume	20

STEP 3. GSA 1

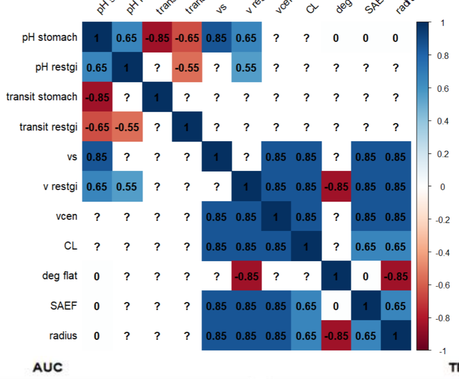


Figure 4. Correlation matrix before the estimation of unknown correlations.

STEP 4. GSA 2

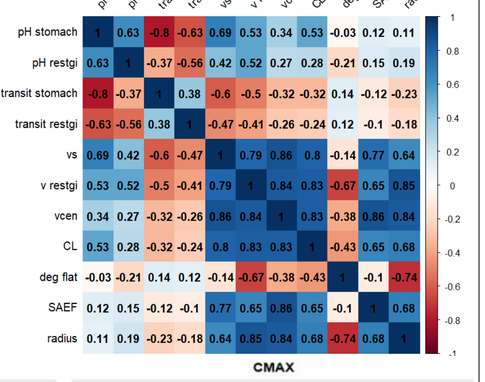


Figure 5. Correlation matrix after the estimation of unknown correlations with the R package mvLognCorr Est [3]

Figure 6. Results of the Two-Stages GSA on AUC, Cmax and Tmax., before (green) and after (pink) applying the correlation matrix . "Sig. level": significance limit.

STEP 5 Parameters' selection

The most significant parameters were Clearance, Central Volume and Stomach transit

METHODOLOGY AND RESULTS

Parameter estimation workflow strategy

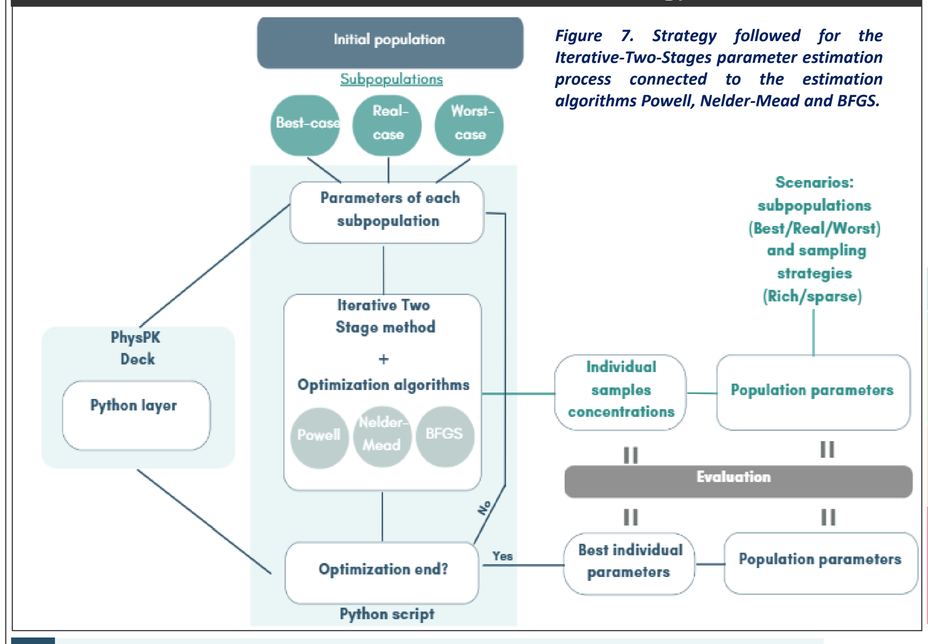


Figure 7. Strategy followed for the Iterative-Two-Stages parameter estimation process connected to the estimation algorithms Powell, Nelder-Mead and BFGS.

STEP 6 Scenario setting

Table 2. Scenario setting according to the virtual population characteristics and the sampling richness (rich: 5 samples, poor: 2 samples)

	Sampling richness	
Population	Rich	Poor
Best-case 25-75th	S1	S4
Real-case 0-10th	S2	S5
Worst-case 0-10/ 90-100th	S3	S6

STEP 7 Implementation of the Iterative Two Stages (ITS)

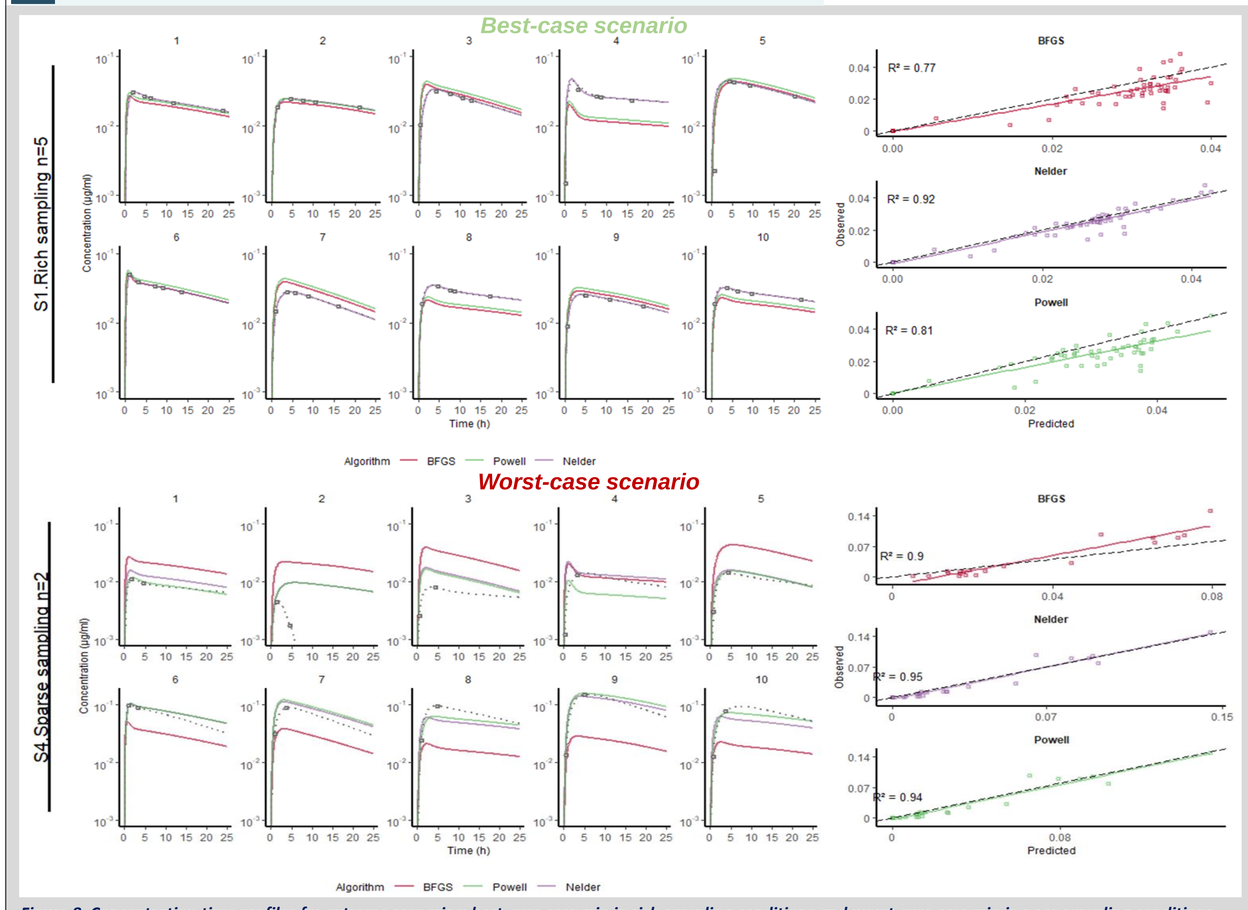


Figure 8. Concentration time profiles for extreme scenarios: best-case scenario in rich sampling conditions and worst-case scenario in poor sampling conditions. Dashed lines correspond to the reference ID profile. The best algorithm was Nelder-Mead and sampling conditions had a higher impact in accuracy and precision.

STEP 8 Evaluation of the GSA+ITS parameter estimation

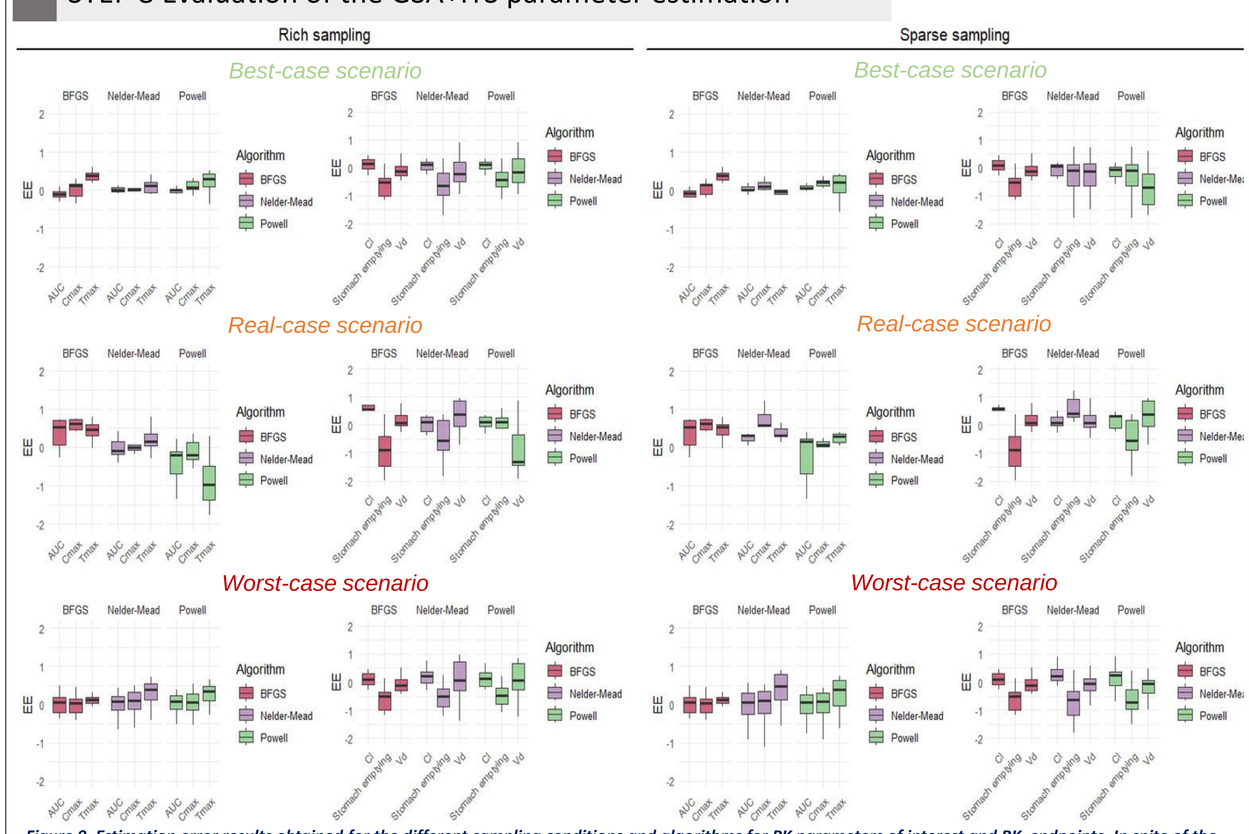


Figure 9. Estimation error results obtained for the different sampling conditions and algorithms for PK parameters of interest and PK endpoints. In spite of the variations in sampling and population PK parameters were adequately estimated in all the scenarios whereas more differences were seen in PK endpoints.

CONCLUSIONS

- **Two-stages δ GSA method offers a robust alternative for evaluating the sensitivity of orally absorbed drugs through PBPK models.**
- **The most relevant parameters in the GSA were clearance, central volume and stomach transit.**
- **Results underscore the importance of incorporating correlations between model inputs and suggest that the Nelder-Mead algorithm may enhance accuracy and precision of parameter estimates**
- **The influence of patient characteristics is significant being thus crucial to keep refining sampling techniques and leverage optimization algorithms to maximize the reliability of PK models.**

References

[1] Cuquerella-Gilabert M et. al; Comput Methods Programs Biomed. 2024
[2] De Carlo A. et al; J Pharmacokinet Pharmacodyn 50, 395–409. 2023
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