Applying A Global Sensitivity Analysis Workflow to Improve Computational Efficiency in Physiologically-Based Pharmacokinetic Modeling

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Introduction

A population physiologically-based pharmacokinetic (PBPK) models usually constructed from dozens of parameters that are affected by uncertainties that can change the model output. The complexity of PBPK models pose a challenge in estimating parameters due to many parameters being unidentifiable. To increase computational efficiency, the current approach is to fix "known" model parameters and only optimize a small subset of parameters. However, this method can lead to problems such as biased estimates for fitted parameters due to correlations/interactions with the fixed parameter. The purpose of this study is to propose a global sensitivity analysis (GSA) workflow which can

- **Reduce PBPK model parameter dimensionality**
- **Reduce the computational burden without introducing bias**
- **Mantain the reliability of parameter estimates and model performance**

Workflow

We applied our workflow to a previously published PBPK model that predicts and characterizes the absorption, distribution, metabolism, and excretion of acetaminophen (APAP) and two major metabolites of APAP-glucuronide and APAP-sulfate in humans [1]. In our GSA workflow, we evaluated three variance-based GSA approach that can calculate both interaction and main effects as sensitivity indices [2, 3, 4]. Moreover, we also applied the "elementary effects" method to compare the sensitivity indices with the variance-based GSA approach and judge the reliability of each method. To understand the time-dependent variation of sensitivity, we examine each index seperately at each time point from 0.5 - 12 hr. We compared the model performance (accuracy and precision) among four different parameter settings as shown in Figure 1.

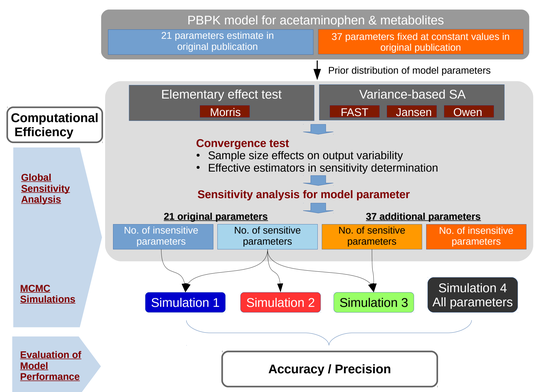

Figure 1: Schematic illustration of the GSA workflow with Bayesian population PBPK modelling

Software and computing platform

This study was fully conducted in an open source environment. Statistical analysis and visualization results were carried out in R v3.4.0. The GSA was performed with R "Sensitivity" package v1.15 [5]. The MCMC simulations and setpoint analyses were conducted using MCSim v5.6 [6]. Parallelizing computation was performed in high performance computing cluster with four chains in CentOS Linux distribution.

Source code

This poster was created using Latex-BeamerPoster.
All source code can find in the github repository: nanhung/GSAposter

Results: Convergence and Computation Time

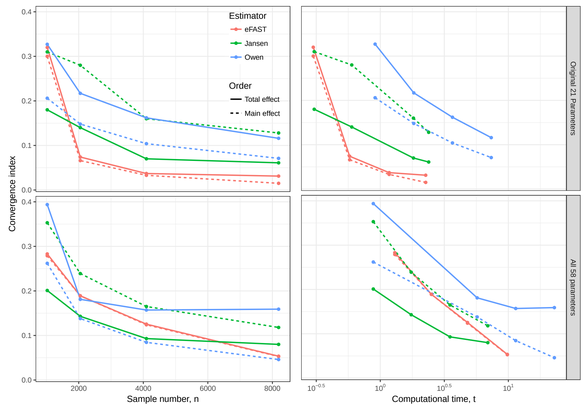

Figure 2: Illustration of the effect of model evaluation on convergence index and computation time (min). The sample size has been increased up from 1024 to 8192 under original 21 and all 58 model parameter settings. In this range of sample size, the eFAST method can lead the expected convergence condition (convergence index < 0.1), rapidly.

Results: GSA for Original Model Parameters

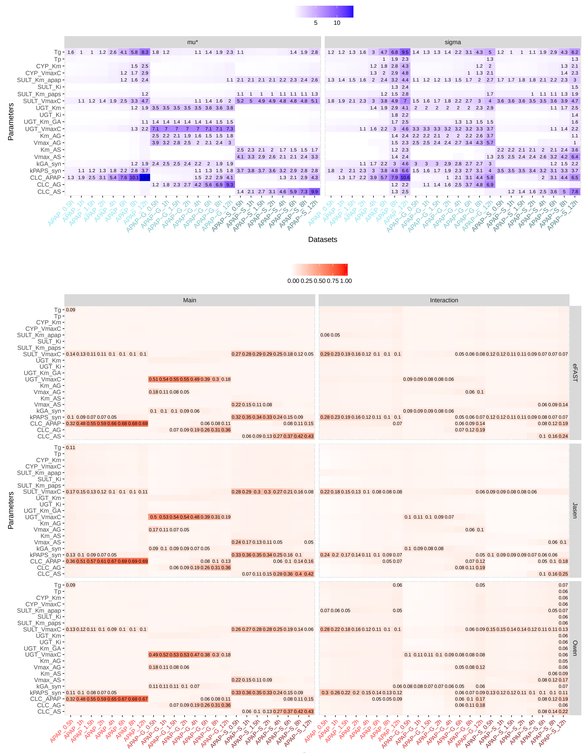

Figure 3: Time-dependent sensitivity coefficients computed through the different GSA methods with parent APAP and its conjugates. The eFAST, Jansen, and Owen (all variance-based methods) generate similar results (bottom pannel). However, the sensitivity properties are different with Morris (Tone-step-at-a-time method)(top pannel). Based on the GSA results from eFAST, we found 11 parameters that influence the model output that Sobol indices were higher than the benchmark (0.05).

Results: GSA for All Model Parameters

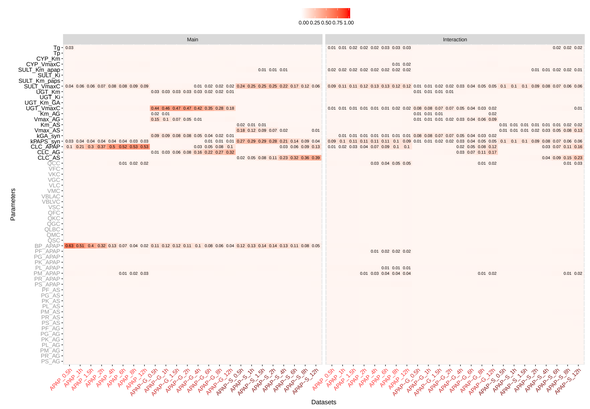

Figure 4: The result of sensitivity analysis of eFAST method that includes 21 original parameters and 37 additional parameters that were fixed in the previous study. All 11 original sensitivity parameter still influence the model output. After incorporating the previously fixed parameters in our analysis, we further detect 9 parameters with Sobol indices higher than the benchmark (0.01).

Evaluation of Posterior Parameter Distribution

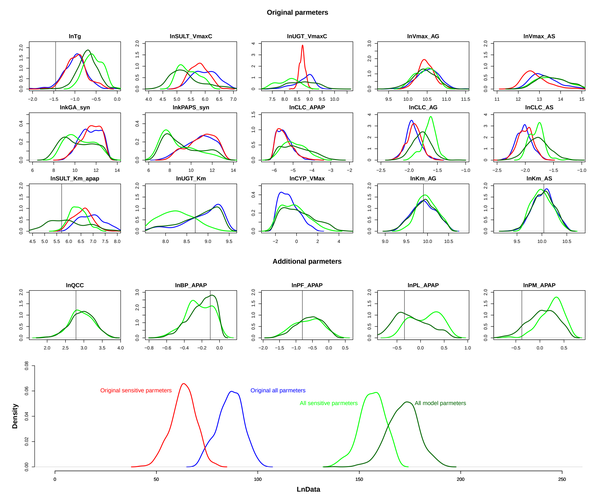

Figure 5: The comparison of the marginal posterior distributions of sensitive parameters and lndata. The result shows the statistical bias when fixing parameter using "expert judgment". The result of lndata shows that the all model parameter setting has the best calibration result, but the "all sensitive parameters" can obtain the better result than original analysis.

Conclusions

- This study obtained the similar results from three different variance-based GSA methods.
- Using eFAST method as GSA approach to determine which parameters to fix and which to estimate can lead to better computational efficiency.
- The current approach can provide better model performance than the traditional judgment method. However, the benchmark used to seperate "sensitive" and "insensitive" parameter may need to be examined to each PBPK model.

Evaluation of Model Performance

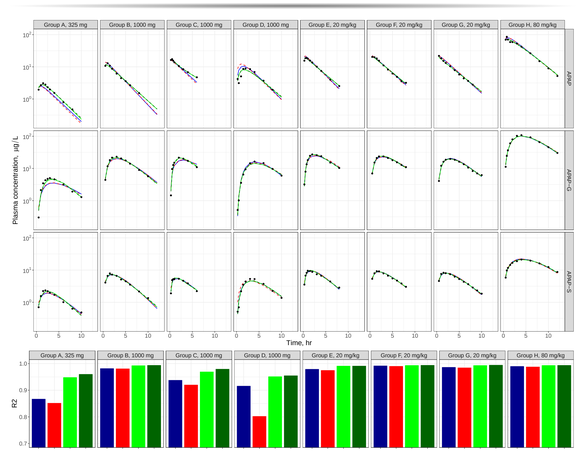

Figure 6: Model evaluation result for the 8 experimental human studies with different APAP dosages. The coefficient of determination (R^2) was used to judge the model performance in each group.

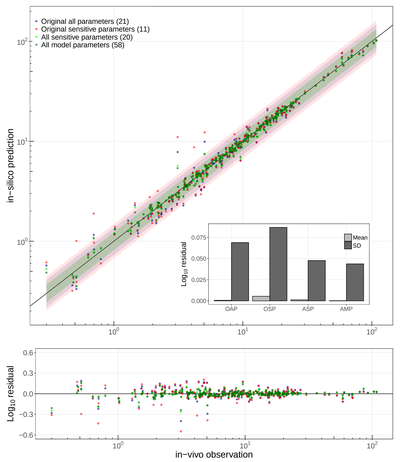

Figure 7: Global evaluation of model fit and model performance. Restricting the MCMC simulation to the sensitive parameters can reduce computational burden while showing little change in model performance. We further find that the simulation from all sensitive parameter (ASP) can provide better precision (residual SD) than original parameters (OAP, OSP) with simulation results for accuracy (residual mean).

The Computational Efficiency for GSA and MCMC

Table 1: Summary of parameter and computational time cost for GSA (n=8,192) and MCMC (n=300,000)

	All parameter	Original estimated	All sensitive	Original sensitive
Number of parameter	58	21	20	11
MCMC (hr)	66.3	37.1	35.2	20.8
GSA (hr) eFAST	-	-	0.164	0.038
Jansen	-	-	0.115	0.040
Owen	-	-	0.382	0.123

Acknowledgements

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