Applying A Global Sensitivity Analysis Workflow to Improve the Computational Efficiencies in Physiologically-Based Pharmacokinetic Model

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Motivations

The population physiologically-based pharmacokinetic (PBPK) model usually constructed from dozens of parameters that are affected by uncertainties and can change the model output. The complexity of PBPK model poses 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 the 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 the PBPK model parameters dimensionality**
- **Reduce the computational burden without introducing bias**
- **Mantain the reliability of parameter estimates and model performance**

Workflow

We applied our published PBPK model for testing, which can predict and characterize the absorption, distribution, metabolism, and excretion of acetaminophen (APAP) with 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 main and total effects as sensitivity indices [2, 3, 4]. Moreover, we also applied the elementary effects method to compare the sensitivity indices from variance-based GSA approach and judge the reliability of each method. To understand the time-dependent variation of sensitivity index, we examine each index in 12-hours after APAP intake as GSA time points. Finally, we compare the model performance (accuracy and precision) among the four different parameter settings.

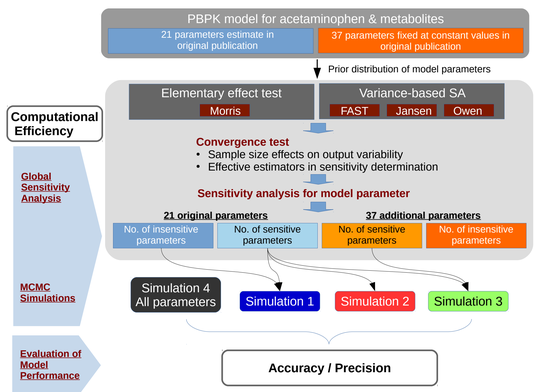

Figure 1: Schematic illustration of the GSA workflow with Bayesian population PBPK modelling

Software and computing platform

This study was fully conduct in 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 making by Latex-BeamerPoster.
All source code can find in the github repository: nanhung/GSAposter

Convergence and Computation Time

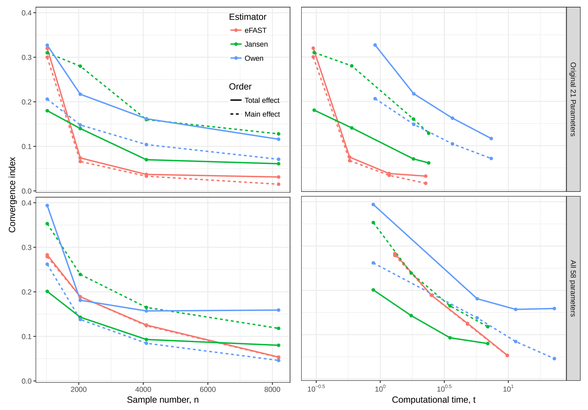

Figure 2: Illustration of the effect of model evaluation on convergence index and computation time (min). The number of sample size has been increased up from 1024 to 8192 under original 21 and all 58 model parameter settings. Under our setting range of sample size, the eFAST method can lead the expected convergence condition, resulting in convergence index less than 0.1.

Sensitivity Analysis for Original Model Parameter

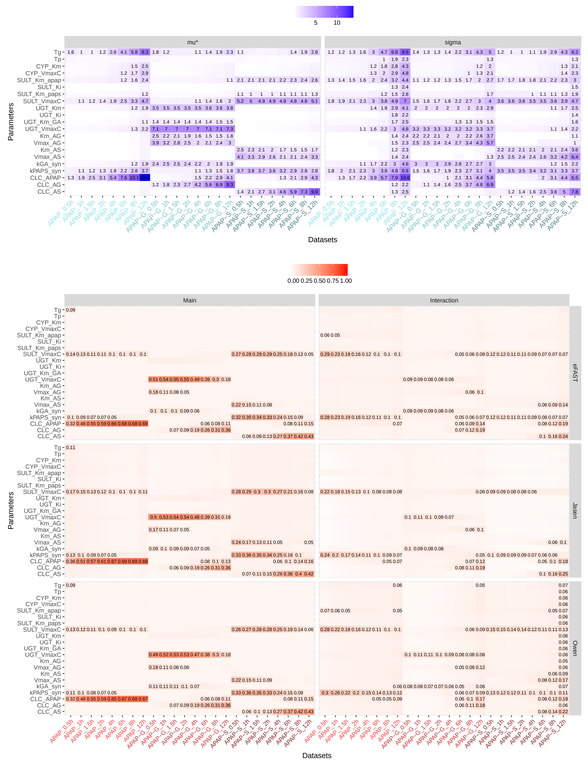

Figure 3: Time-dependent sensitivity coefficients computed through the different GSA methods with parent APAP and its conjugates. We can obtain that eFAST, Jansen, and Owen (variance-based method) can generate similar results. However, the sensitivity properties are different with Morris (one-step-at-a-time method). According to the GSA result from eFAST, we found 11 parameters that influence the model output that Sobol indices were higher than the benchmark (0.05).

Sensitivity Analysis for All Model Parameter

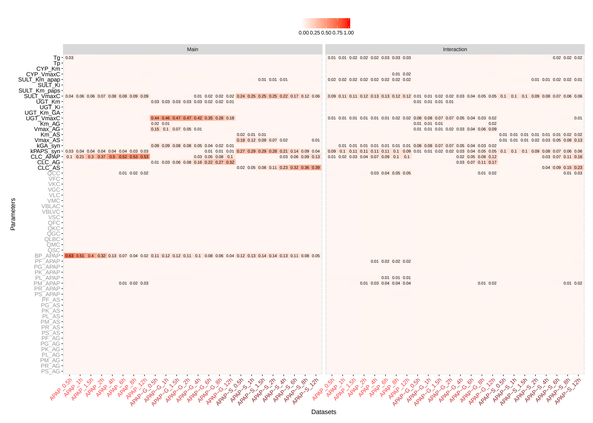

Figure 4: The result of sensitivity analysis of eFAST method that includes the original 21 original model parameters and 37 additional parameters that were fixed in the previous study. All 11 original sensitivity parameter still influence the model output. After incorporating the previously fixed parameters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

Evaluation of Model Parameter

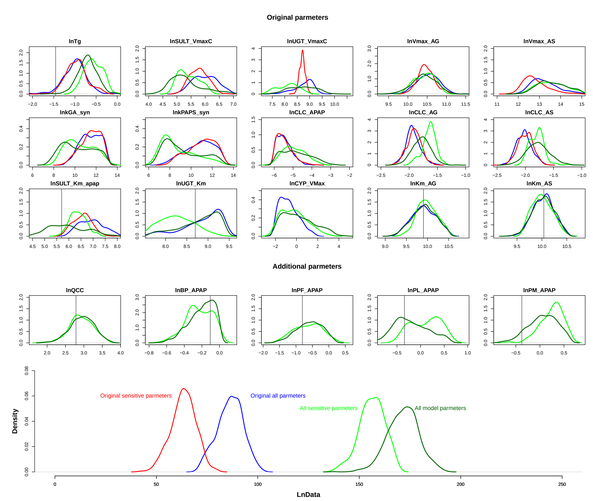

Figure 5: The comparison of the marginal posterior distribution of sensitive parameters and lndata. The result shows the statistical bias among four different parameter settings. The result of lndata shows that the all model parameter setting has the best calibration result. Moreover, the current study can provide the better calibration result than original all parameter setting when only consider the sensitive parameter in PBPK model.

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, we still need to clarify the reliable/robust benchmark that can use to do parameter screening.

Evaluation of Model Performance

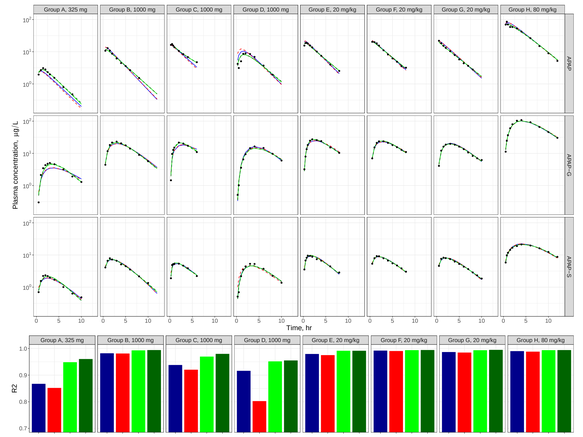

Figure 6: Model evaluation result for the 8 experimental human studies with different APAP dosages. The determination coefficient (R^2) was used to judge the model performance in each group.

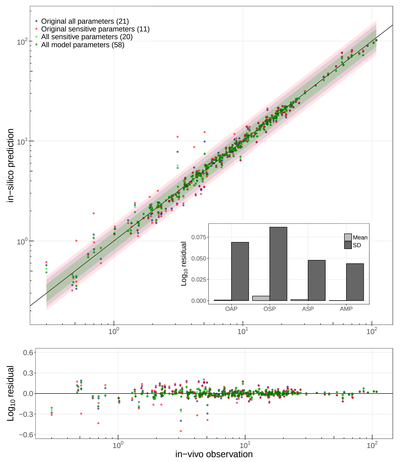

Figure 7: Global evaluation of model fit and model performance. Restricting the MCMC simulation to the sensitive parameters can reduce computational burden while showing little change in model performance. We further find that the simulation from all sensitive parameter (ASP) can provide better precision (residual SD) than original setting. However, it cannot provide the same test result in 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)	20.8	35.2	66.3	37.1
GSA (min) eFAST	-	-	9.83	2.26
Jansen	-	-	6.91	2.39
Owen	-	-	22.9	7.36

Acknowledgements

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