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

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INTRODUCTION

Traditionally, the solution to reduce parameter dimensionality in a physiologically-based pharmacokinetic (PBPK) model is through expert judgment. However, this approach may lead to bias in parameter estimates and model predictions if important parameters are fixed at uncertain or inappropriate values.

The purpose of this study was to explore the application of global sensitivity analysis (GSA) to ascertain which parameters in the PBPK model are non-identifiable, and therefore can be assigned fixed values in Bayesian parameter estimation with minimal bias.

HYPOTHESIS

Our study hypothesis is that *GSA can* ***provide a systematic method to ascertain which PBPK model parameters have negligible influence on model outputs and can be fixed to improve computational speed in Bayesian parameter estimation with minimal bias***. Although GSA offers many advantages compared to local SA, only a few applications in PBPK modeling have been published. For instance, a previous study for a PBPK model of *m*-Xylene demonstrated that parameters identified by GSA as having little influence had similar posterior distributions to those when all parameters were calibrated using the Bayesian approach [1]. Here, we extend this approach in a new case study using a more complex model: a PBPK model for acetaminophen (APAP) and its conjugated metabolites. We used this case study to answer four key questions:

(1) What is the relative computational efficiency/rate of convergence of various GSA algorithms?
(2) Do different algorithms give consistent results as to direct and indirect parameter sensitivities?
(3) Can we identify "insensitive" parameters that can be fixed in a Bayesian PBPK model while achieving similar degrees of accuracy and precision?
(4) Does fixing parameters using "expert judgment" lead to unintentional imprecision or bias?

We examined questions (1) and (2) by applying four different GSA algorithms to the PBPK model. For question (3), we compared the results of MCMC simulations of the PBPK model with and without fixing sensitive parameters. We applied each of these analyses to the PBPK model using the original set of model parameters (OMP), calibrated in the previously published model, which included numerous parameters fixed by expert judgment; the sensitive subset of these original parameters (OSP); the full set of model parameters (FMP) including those previously fixed; and the sensitive subset of these parameters (FSP). Thus, question (4) was examined by comparing the results obtained from OMP, OSP, FMP, and FSP.

MATERIALS & METHODS

➢ **APAP-PBPK Model, Parameters, and Data**

Our analysis made use of our previously developed PBPK model that describes the ADME of APAP and its conjugated metabolites, APAP-glucuronide (APAP-G) and APAP-sulfate (APAP-S) in humans [2,3]. Distributions for parameter priors were derived from literature values and were assumed to be uniform or truncated normal distributions under the log-transformed scale [2,4,5].

➢ **GSA Algorithms and Approach**

We compared the elementary effect-based Morris method and three estimators for the variance-based Sobol index in their ability to distinguish "sensitive" parameters to be estimated and "insensitive" parameters to be fixed. We first check the convergence of sensitivity indices through the method from Sarrazin et al. [6] and applied GSA to the original published model, comparing Bayesian model calibration results using all the original model parameters (OMP) versus the subset of original sensitive parameters (OSP). We then applied GSA to all the PBPK parameters, including those fixed in the published model, comparing the model calibration results using this *full set* of model parameters (FMP) versus the *full set sensitive* parameters (FSP). We also examined the impact of different cut-off points (0.01 and 0.05) to distinguish the sensitive and insensitive parameters.

➢ **MCMC Simulations**

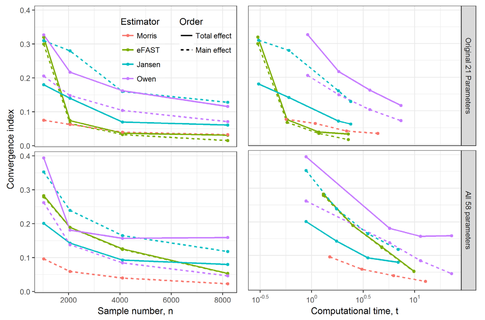
We evaluated global parameter sensitivity both for the OMP alone, as well as the FMP. As a benchmark, the Bayesian-PBPK analysis was initially performed for both the OMP and FMP, recording baseline values for computational time and model performance.

➢ **Software and Computing Platform**

- GSA was performed with the R "sensitivity" package v.1.15 [7].
- The MCMC simulations were conducted using MCSim v.5.6 [8].
- Parallelized computation of the MCMC was performed within the CentOS Linux distribution on a high-performance computing cluster at Texas A&M University.

RESULTS

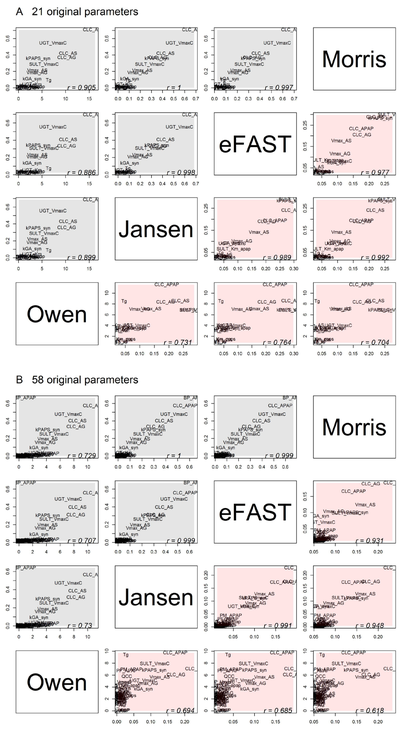
Convergence Analysis of Sensitivity Indices



In each case, the maximum index (i.e., combination of time-point, dataset, parameter, compound, and main vs. total effect that converges the slowest) is shown, along with the cost in terms of number of model evaluations and computational time. For the Morris screening method, the analysis with the small sample number of 1024 (resulting in 22,528 model evaluations) reached an acceptable converged result (convergence index < 0.1), The alternative methods of Jansen and Owen estimators did not lead to convergence, even up to a sample number of 8192.

Answer 1: The Morris method provided the most efficient computational performance and convergence result, followed by eFAST.

Correlation Matrix for Main (grey) and Interaction (red) Effects



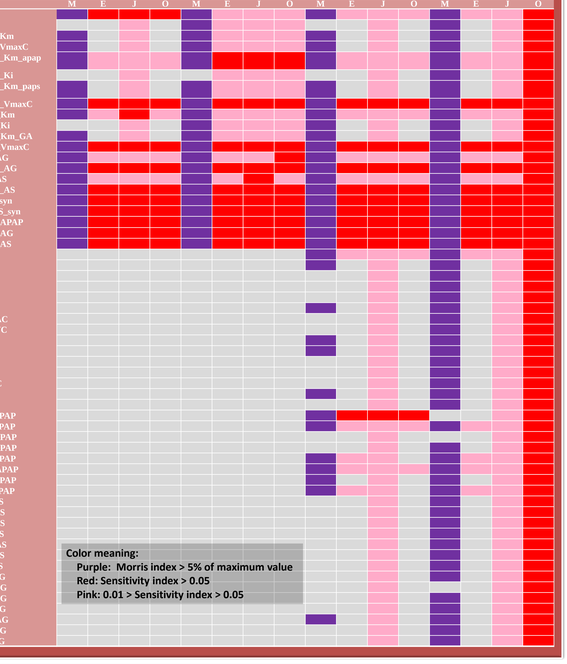
A
For the OMP, the variance-based Sobol indices showed a high correlation (r > 0.9) with each other. The Morris indices had the relatively lower correlation with variance-based indices. In addition, the correlation of the interaction had a lower range (0.70 – 0.99) than the main effects (0.88 – 1.00). The correlation plot for the Morris- and variance-based indices shows a 'hockey stick' shape, suggesting that there are different correlation properties between "sensitive" and "insensitive" parameters.

B
The FMP shows similar correlation properties for the sensitivity indices.

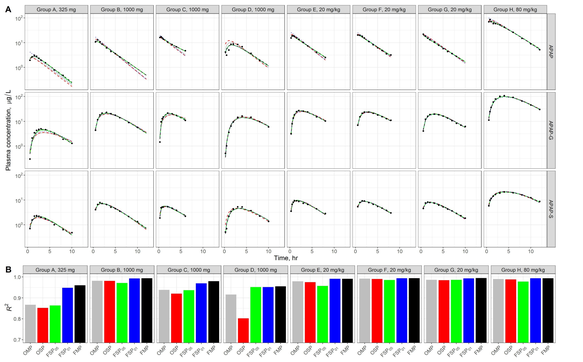
Answer 2: Local and global method give inconsistent results as to direct and indirect parameter sensitivities.

Parameter-Specific Sensitivity Test Result

The parameter-specific sensitivity test result for OMP and FMP settings by GSA methods. The lack of convergence, along with the inconsistencies seen with the OMP, led us to focus on the eFAST method as representing the best balance among reliability, efficiency, and the ability to discriminate between sensitive and insensitive parameters.

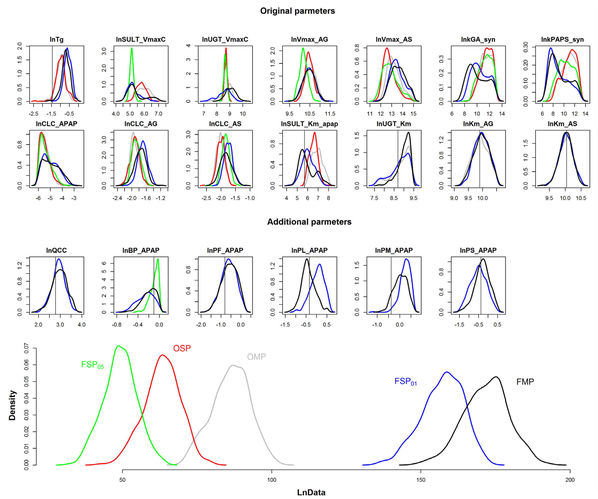


Model Evaluation Across Different Analyses for Each Study Group



A. Visual inspection of the data points relative to the scatter of the predictions suggests that each parameter set shows a consistent or similar predicted curve in the high-dosage (20 mg/kg and 80 mg/kg) groups (E to H). The low-dose groups (325 mg and 1000 mg) (A to D) showed slightly different calibration results in the predicted curves from the given parameter set. We used the coefficient of determination (R^2) as a metric of precision.
B. Results show that the estimated R^2 were relatively high in all simulation sets (R^2 >0.7). Across all the different analyses, the best performance was from the FMP and the "sensitive" parameters FSP_{01} (all estimated R^2 > 0.9) – higher than the results from the OMP, OSP, or FSP_{05}.

Comparison of the Marginal Posterior Distributions for Sensitive Parameter and Log-likelihood

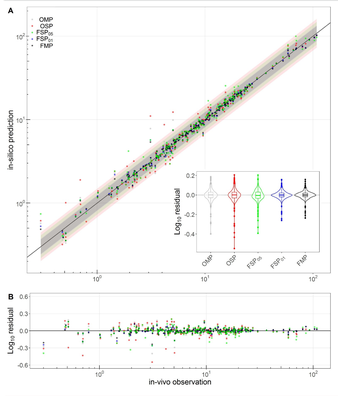


Some parameters showed similar distributions among different analyses. However, for some parameters, such as the partition coefficient of muscle (PM_APAP), the fixed nominal value was closer to the tail of the posterior distribution. Thus, fixing parameters using "expert judgment" can lead to bias in some of the parameter estimates.

For OMP and OSP, the log-likelihood distributions overlapped, indicating similar model fit. The log-likelihood distribution for FSP_{05} was substantially below both the OMP and FMP. However, for FSP_{01}, using the cut-off of 0.01, not only did the log-likelihood distribution overlap with FMP, based on all the parameters, but it was also substantially greater than the log-likelihood using the OMP.

Answer 4:
GSA was more effective than "expert judgment" at identifying parameters that are influential, and led to a better fit between predictions and data *even though almost the same number of parameters were used* .

Global Evaluation of the Model Performance and Computational Efficiency



A
compares the overall global evaluation of model fits across all the alternative analyses.

B
The residuals from the predicted result versus experimental values were used to evaluate the **"accuracy"** and **"precision"** of model performance.

		OMP	FMP
Number of parameters		21	58
MCMC time-cost (hr)		37.1	66.3
GSA-EE (hr)	Morris	0.009	0.019
GSA-Sobol (hr)	eFAST	0.164	0.038
	Jansen	0.115	0.04
	Owen	0.382	0.123
Sensitivity cut-off point > 0.05		**OSP**	**FSP_{05}**
Number of parameters		11	10
MCMC time-cost (hr)		20.8	22.1
Sensitivity cut-off point > 0.01		**(=OMP)**	**FSP_{01}**
Number of parameters		21	20
MCMC time-cost (hr)		37.1	35.2

The above table summaries the time-cost in GSA and MCMC analyses as the measurement of computational efficiency.

Answer 3: We found that restricting the MCMC simulations to the sensitive parameters can substantially reduce computational burden while showing little change in model performance.

TAKE-HOME MESSAGE

Our results suggest the following efficient workflow for applying GSA to Bayesian PBPK [9]:

(1) Establish prior distributions for all parameters, and ensure that the prior predictions cover the range of data being used for model calibration.
(2) Use the eFAST estimator for parameter sensitivity, making sure to check convergence using the method of Sarrazin et al. (2016).
(3) Visualize parameter sensitivity, distinguishing "sensitive" and "insensitive" parameters with a cut-off such as 0.01 or 0.05, so that any parameter with a Sobol index for at least one output greater than the cut-off would be identified as "sensitive." The cut-off approach to identify and classify parameters could also be implemented in software once reasonable threshold values are established.
(4) Conduct model calibration using MCMC simulation for only the "sensitive" parameters, fixing "insensitive" parameters at nominal values.

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