

## 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 &amp; METHODS

## &gt; 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].

## &gt; 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.

## &gt; 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.

## &gt; 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.

