



TEXAS A&M UNIVERSITY

Veterinary Medicine
& Biomedical Sciences

pksensi: an R package to apply sensitivity analysis in pharmacokinetic modeling

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INTRODUCTION

- Sensitivity analysis is a mathematical technique to investigate how variations in model parameters affect model outputs. An increasing number of studies use global sensitivity analysis (GSA) to determine which model parameters contribute to high variation in model predictions. This technique has also been applied in pharmacology and toxicology research [1,2], including pharmacokinetic modeling, which describes the changes in the concentrations or amounts of a substance in several tissues over time. These tissues are represented by individual compartments (space) under the assumption that the drug is homogeneously distributed within the same compartment.
- One goal of sensitivity analysis in pharmacokinetic research is to examine the sensitivity of output variables (e.g. compound concentration in blood or tissues) that affected by input parameters, such as anatomical, physiological, and kinetic constants [2]. It can be further applied to parameter prioritization and parameter fixing before model calibration [3].

- In our previous work [3], we developed an approach to apply GSA in order to reduce the computational burden in the Bayesian, Markov Chain Monte Carlo (MCMC)-based calibration process of a physiologically based pharmacokinetic (PBPK) model. We used GNU MCSim [4], an effective simulation package for Bayesian population PBPK modeling, to calibrate the model. We found that the extended Fourier Amplitude Sensitivity Test (eFAST), a type of variance-based GSA algorithm, had the best balance of efficiency and accuracy for a complex, multi-compartment, multi-dataset, and multi-metabolite PBPK model. Also, we developed some effective visualization approaches that can be used to distinguish between "influential" and "non-influential" parameters through "cut-off" of sensitivity index. We also developed a useful approach for communicating the parameter sensitivity in decision making.

APPROACH

We present here an R package, called **pksensi**, which is designed to make sensitivity analysis more accessible and reproducible in pharmacological and toxicological research. This package can investigate both parameter uncertainty and sensitivity in pharmacokinetic models, including PBPK, and advanced compartment absorption and transit models with multivariate model output. The design concepts of **pksensi** are:

- Cross-platform: Models can run on Windows/MacOS/Linux**
- Freedom: All related packages are free and open source**
- Integration: Users can run pharmacokinetic models in R with scripts written in C or GNU MCSim**
- Decision support: The output results and visualization tools can be used to easily determine which parameters have "non-influential" effects on the model output and can be fixed in model calibration.**

INSTALLATION AND FUNCTIONS

```
# To install pksensi, you can use following method (in R):
install.packages("pksensi") # get latest version from CRAN
remotes::install_github('nanhung/pksensi', upgrade=T) # get the development version from GitHub
```

Workflow	Function	Description
Installation	mcsim_install	Download and install the specific version of MCSim
	mcsim_version	Check MCSim version
Compilation	model_compile	Compile MCSim model code
PK modeling	rfast99	Create the sequences for each parameter by eFAST
	generate_infile	Generate MCSim input file
	solve_mcsim	Solve ODE through MCSim
Visualization & decision making	solve_fun	Solve ODE through R deSolve package
	pksim	PK plot of the outputs based on the given parameter (Uncertainty analysis)
	plot	Time-dependent sensitivity (with 95 % CI)
Parameter generation	check	Check sensitivity measurement for parameter fixing
	heat_check	Create heatmap to overview the result of GSA

WORK FLOW

