



TEXAS A&M UNIVERSITY

Veterinary Medicine
& Biomedical Sciences

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

Nan-Hung Hsieh¹, Brad Reisfeld², Weihsueh A. Chiu¹¹Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, TX 77845, USA² Chemical and Biological Engineering & School of Biomedical Engineering, Colorado State University, Fort Collins, CO 80521, USA

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]. Pharmacokinetic modeling describes the changes in the concentrations or amounts of a substance within model compartments over time. The goal of sensitivity analysis in pharmacokinetic research is to examine the sensitivity of output variables (e.g. compound concentration in blood or tissues) in pharmacokinetic models responds to 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 global sensitivity analysis workflow 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 global sensitivity analysis algorithm, had the best balance of efficiency and accuracy for a complex, multi-compartment, multi-dataset, and multi-metabolite PBPK model. Also, we found some efficient visualization approaches that can be used to distinguish between "influential" and "non-influential" parameters. We also found a useful approach for communicating the parameter sensitivity in decision making.

MOTIVATIONS

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

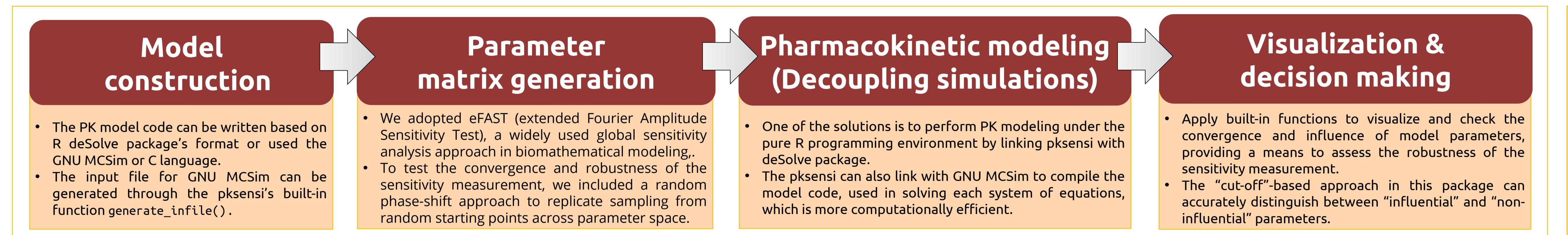
- Cross-platform: Models can run on Windows/MacOS/Linux**
- Freedom: All related packages are free and open source**
- Integrated application: Users can run pharmacokinetic models in R with script that were written in C or GNU MCSim**
- Decision making: The output results and visualization tools can 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

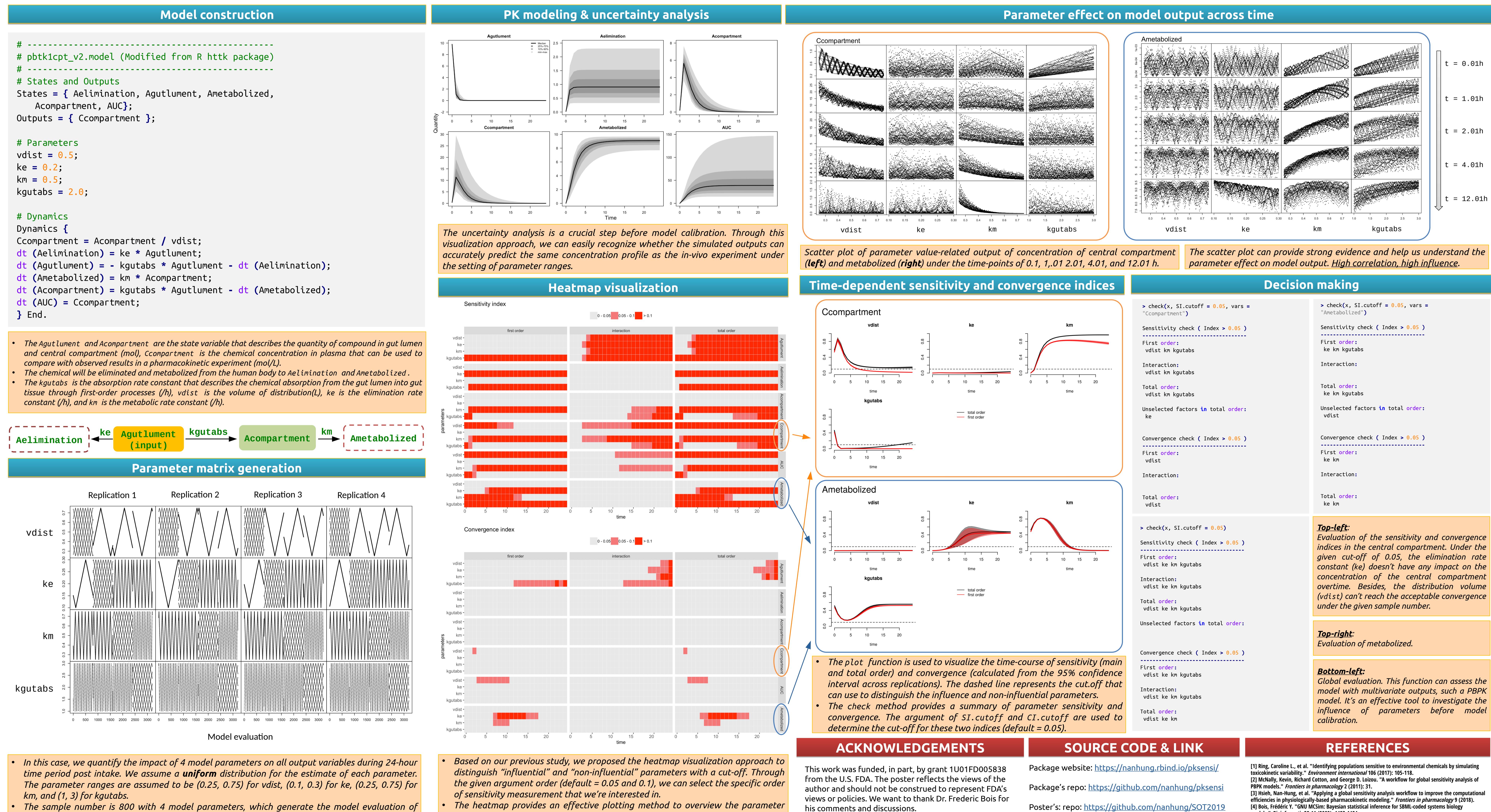
```
# To install pksensi, you can use following method (in R):
install.packages("pksensi") # get latest version from CRAN
install_github("nanhung/pksensi") # get the development version from GitHub
```

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)
Workflow	check	Check sensitivity measurement for parameter fixing
	heat_check	Create heatmap to overview the result of GSA

WORK FLOW



EXAMPLE (One-compartment PBTK model)



ACKNOWLEDGEMENTS

This work was funded, in part, by grant 1U01FD005838 from the U.S. FDA. The poster reflects the views of the author and should not be construed to represent FDA's views or policies. We want to thank Dr. Frederic Bois for his comments and discussions.

SOURCE CODE & LINK

Package website: <https://nanhung.rbind.io/pksensi/>
Package's repo: <https://github.com/nanhung/pksensi>
Poster's repo: <https://github.com/nanhung/SOT2019>

REFERENCES

- [1] Ring, Caroline L., et al. "Identifying populations sensitive to environmental chemicals by simulating their pharmacokinetics." *Environmental Health Perspectives* 108 (2000): 105-116.
- [2] Michael, Kevin, Richard Cotton, and George E. Lopez. "A workflow for global sensitivity analysis of PBPK models." *Frontiers in pharmacology* 2 (2011): 31.
- [3] Hsieh, Nan-Hung, et al. "Applying a global sensitivity analysis workflow to improve the computational efficiency of physiologically based pharmacokinetic modeling." *Frontiers in pharmacology* 9 (2018).
- [4] Pepe, Frederic, and MCSim. "A guide to MCSim: Bayesian statistical inference for SMT-coded systems biology models." *Bioinformatics* 25, 5.11 (2009): 1453-1454.
- [5] Pearce, Robert G., et al. "HTTK: R package for high-throughput toxicokinetics." *Journal of statistical software* 79 (2017): 1.