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:

1. **Cross-platform: Models can run on Windows/MacOS/Linux**
2. **Freedom: All related packages are free and open source**
3. **Integration: Users can run pharmacokinetic models in R with scripts written in C or GNU MCSim**
4. **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 in 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 verson of MCSim
	`mcsim_version`	Check MCSim version
Compilation	`model_compile`	Compile MCSim model code
Parameter generation	`rfast99`	Create the sequences for each parameter by eFAST
PK modeling	`generate_infile`	Generate MCSim input file
	`solve_mcsim`	Solve ODE through MCSim
	`solve_fun`	Solve ODE through R deSolve package
Visualization & decision making	`pksim`	PK plot of the outputs based on the given parameter (Uncertainty analysis)
	`plot`	Time-dependent sensitivity (with 95 % CI)
	`check`	Check sensitivity measurement for parameter fixing
	`heat_check`	Create heatmap to overview the result of GSA

WORK FLOW

Model construction

- The PK model code can be written based on R deSolve package's format or using GNU MCSim or C language.
- The input file for GNU MCSim can be generated through the pksensi's built-in function `generate_infile()`.

Parameter matrix generation

- We adopted eFAST (extended Fourier Amplitude Sensitivity Test), a widely used global sensitivity analysis approach in biomathematical modeling,.
- To test the convergence and robustness of the sensitivity measurement, we included a random phase-shift approach to replicate sampling from random starting points across parameter space.

Pharmacokinetic modeling (Decoupling simulations)

- One of the solutions is to perform PK modeling under the pure R programming environment by linking pksensi with deSolve package.
- The pksensi can also link with GNU MCSim to compile the model code, used in solving each system of equations, which is more computationally efficient.

Visualization & decision making

- Apply built-in functions to visualize and check the convergence and influence of model parameters, providing a means to assess the robustness of the sensitivity measurement.
- Distinguish parameters with a "cut-off", so that any parameter with a sensitivity index for selected output(s) greater than the cut-off over time would be identified as "influential."

FUTURE DIRECTIONS

1. **This package is still experimental and maturing, we are continuous improving its function and collecting user feedback. Your comments are very valuable!**
2. **In addition to the eFAST method, we will add the Sobol method (variance-based sensitivity analysis) in this package and compare the usability with eFAST.**
3. **Also, we'll integrate pksensi to other R packages to make it more practical for R users.**

EXAMPLE (One-compartment PBTK model)

Model construction

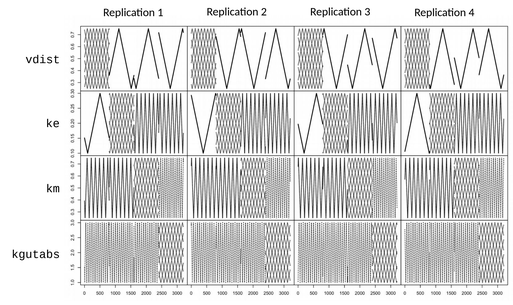
```
# ------------------------------------------------
# pbtk1cpt_v2.model (Modified from R httk package)
# ------------------------------------------------
# States and Outputs
States = { Aelimination, Agutlument, Ametabolized,
       Acompartment, AUC};
Outputs = { Ccompartment };

# Parameters
vdist = 0.5;
ke = 0.2;
km = 0.5;
kgutabs = 2.0;

# Dynamics
Dynamics {
Ccompartment = Acompartment / vdist;
dt (Aelimination) = ke * Agutlument;
dt (Agutlument) = - kgutabs * Agutlument - dt (Aelimination);
dt (Ametabolized) = km * Acompartment;
dt (Acompartment) = kgutabs * Agutlument - dt (Ametabolized);
dt (AUC) = Ccompartment;
} End.
```

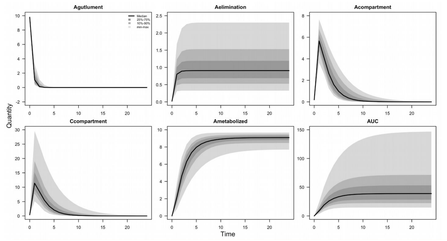
- *The `Agutlument` and `Acompartment` are the state variables that describes the quantity of compound in gut lumen and central compartment (mol), `Ccompartment` is the chemical concentration in plasma that can be used to compare with observed results in a pharmacokinetic experiment (mol/L).*
- *The chemical will be eliminated and metabolized from the human body to `Aelimination` and `Ametabolized`.*
- *The `kgutabs` is the absorption rate constant that describes the chemical absorption from the gut lumen into gut tissue through first-order processes (/h), `vdist` is the volume of distribution(L), `ke` is the elimination rate constant (/h), and `km` is the metabolic rate constant (/h).*

Parameter matrix generation



- *In this case, we quantified the impact of 4 model parameters on all output variables during a 24-hour time period post dose intake. We assumed a **uniform** distribution for the estimate of each parameter. The parameter ranges were assumed to be (0.25, 0.75) for `vdist`, (0.1, 0.3) for `ke`, (0.25, 0.75) for `km`, and (1, 3) for `kgutabs`.*
- *The sample number was 800 with 4 model parameters, which generated 3,200 model evaluations. The replication was set to 20. The above figure only plotted for 4 replications.*

PK modeling & uncertainty analysis

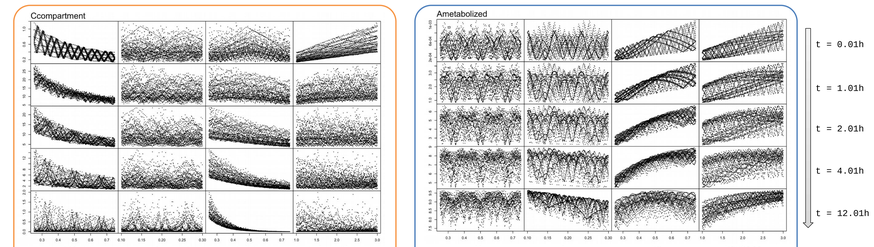


The uncertainty analysis is a crucial step prior model calibration. Through this visualization approach, we can easily recognize whether the simulated outputs can accurately predict the same concentration-time profile observed in the clinical setting within a tested range of parameters of interest.

Heatmap visualization

- *Based on our previous study, we proposed the heatmap visualization approach to distinguish "influential" and "non-influential" parameters with a cut-off. Through the given argument order (default = 0.05 and 0.1), we can select the specific order of sensitivity measurement that we're interested in.*
- *The heatmap provides an effective plotting method to overview the parameter influence and convergence (red area in heatmap).*

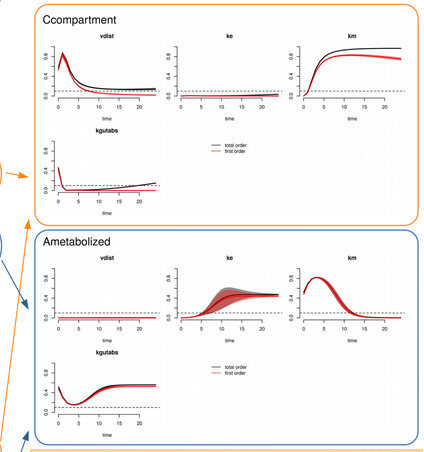
Parameter effect on model output across time



*Scatter plot of parameter value-related output of concentration of central compartment **(left)** and metabolized (**right**) under the selected time-points.*

*The scatter plot provides evidence of parameter influence and help us understand the parameter effect on model output. **High correlation, high influence**.*

Time-dependent sensitivity and convergence indices



- *The `plot` function is used to visualize the time-course of sensitivity (main and total order) and convergence (calculated from the 95% confidence interval across replications). The dashed line represents the cut.off that can use to distinguish the influence and non-influential parameters.*
- *The `check` method provides a summary of parameter sensitivity and convergence. The argument of `SI.cutoff` and `CI.cutoff` are used to determine the cut-off for these two indices (default = 0.05).*

Decision making

```
> check(x, SI.cutoff = 0.05, vars =
"Ccompartment")

Sensitivity check ( Index > 0.05 )
-----------------------------------
First order:
 vdist km kgutabs

Interaction:
 vdist km kgutabs

Total order:
 vdist km kgutabs

Unselected factors in total order:
 ke


Convergence check ( Index > 0.05 )
-----------------------------------
First order:
 vdist

Interaction:


Total order:
 vdist
```

```
> check(x, SI.cutoff = 0.05, vars =
"Ametabolized")

Sensitivity check ( Index > 0.05 )
-----------------------------------
First order:
 ke km kgutabs

Interaction:


Total order:
 ke km kgutabs

Unselected factors in total order:
 vdist


Convergence check ( Index > 0.05 )
-----------------------------------
First order:
 ke km

Interaction:


Total order:
 ke km
```

```
> check(x, SI.cutoff = 0.05)

Sensitivity check ( Index > 0.05 )
-----------------------------------
First order:
 vdist ke km kgutabs

Interaction:
 vdist ke km kgutabs

Total order:
 vdist ke km kgutabs

Unselected factors in total order:


Convergence check ( Index > 0.05 )
-----------------------------------
First order:
 vdist ke km kgutabs

Interaction:
 vdist ke km kgutabs

Total order:
 vdist ke km
```

***Top-left**:*
Evaluation of the sensitivity and convergence indices in the central compartment. Under the given cut-off of 0.05, the elimination rate constant (ke) does not have any impact on the concentration of the central compartment overtime. Additionally, the distribution volume (vdist) cannot reach acceptable convergence under the given sample number.

***Top-right**:*
Evaluation of metabolized.

***Bottom-left**:*
Global evaluation. This function can assess the model with multivariate outputs, such a PBPK model. It's an effective tool to investigate the influence of parameters before model calibration.

ACKNOWLEDGEMENTS

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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

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