Package ‘pksensi’

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Title  Global Sensitivity Analysis in Physiologically Based Kinetic Modeling
Version  1.2.3
Description  Applying the global sensitivity analysis workflow to investigate the parameter uncertainty and sensitivity in physiologically based kinetic (PK) models, especially the physiologically based pharmacokinetic/toxicokinetic model with multivariate outputs. The package also provides some functions to check the convergence and sensitivity of model parameters. The workflow was first mentioned in Hsieh et al., (2018) <doi:10.3389/fphar.2018.00588>, then further refined (Hsieh et al., 2020 <doi:10.1016/j.softx.2020.100609>).
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**Description**

Applying a global sensitivity analysis approach to reduce parameter dimensionality in physiologically based kinetic modeling and evaluate the robustness of the algorithm under the given sampling number.

**Details**

The "extended Fourier amplitude sensitivity testing (eFAST)", a variance-based sensitivity analysis method is used to estimate the parameter impact on model output (Saltelli et al. 1999). The eFAST is the effective algorithm to determine the influential parameter in physiologically-based pharmacokinetic model calibration (Hsieh et al. 2018). The eFAST algorithm is sourced from sensitivity package but implemented the random-phase shift to evaluating the robustness of sensitivity measurement under the given sample size.

**References**


**Pharmacokinetic Dataset of Acetaminophen**

**Description**

The Acetaminophen dataset contains a human experiment of pharmacokinetic data for acetaminophen and its major metabolites acetaminophen-glucuronide and acetaminophen-sulfate.

**Usage**

**Format**

A data frame containing the following columns:

- **Wt**: averaged weight of the study population (kg).
- **Dose**: given oral dose of acetaminophen administered (mg/kg).
- **Time**: time after drug administration (hr).
- **APAP**: concentration of acetaminophen in the sample (mg/L).
- **AG**: concentration of acetaminophen-glucuronide in the sample (mg/L).
- **AS**: concentration of acetaminophen-sulfate in the sample (mg/L).
- **Study**: sourced reference.

**References**


**Check**

**Check the Parameter Sensitivity**

**Description**

Visualize and check the sensitivity (or convergence) measurement with the given result.
check(x, times, vars, cutoff, out)

heat_check(
  x,
  order = c("first order", "interaction", "total order"),
  vars = NULL,
  times = NULL,
  index = "SI",
  cutoff = c(0.05, 0.1),
  level = T,
  text = F,
  show.all = FALSE
)

## S3 method for class 'rfast99'
plot(x, vars = 1, cutoff = 0.1, ...)

## S3 method for class 'rfast99'
print(x, ...)

Arguments

- **x**: a list of the storing information in the defined sensitivity function.
- **times**: a logical value or character to specify the display time in simulation.
- **vars**: a logical value or character to specify the display variable in simulation.
- **cutoff**: a value or vector to set the cut-off for sensitivity (or convergence) index. The default is 0.05 and 0.1.
- **out**: a logical value to print the checking result to the console.
- **order**: a vector of the interested output index, including first order, interaction, and total order.
- **index**: a character to choose sensitivity index SI (default) or convergence index CI.
- **level**: a logical value to use continuous or discrete (default) output.
- **text**: a logical value to display the calculated indices in the plot.
- **show.all**: a logical value to show all testing parameters in the heatmap. The default is set to FALSE to show only the influential parameters.
- **...**: additional arguments to customize the graphical parameters.

Details

The convergence of sensitivity indices for each parameter is using the approach proposed by Sarrazin et al. (2016). This method quantitatively assesses the convergence by computing the range of 95% Using the global approach based on the heatmap visualization combined with the index "cutoff," can systematically distinguish between "influential" and "non-influential" parameters (Hsieh et al. 2018).
Value

The print function returns sensitivity and convergence indices with given time-step in the console. The check method provides the summary of parameter sensitivity and convergence according to the given cutoff. It can distinguish the influential and non-influential parameter by the providing value of cutoff. The plot function can generate the time-course functional outputs of first order and interaction indices for each parameter. The default output is the first model variable. The heat_check provides a convenient way to visualize and distinguish the influential and non-influential parameter by the setting cut-off. The convergence index can examine the stability of the sensitivity index. To check convergence, be sure to conduct the replication in rfast99.

References


See Also

tell2

Examples

```r
q <- "qunif"
q.arg <- list(list(min = 0.6, max = 1),
             list(min = 0.5, max = 1.5),
             list(min = 0.02, max = 0.3),
             list(min = 20, max = 60))
params <- c("F","KA","KE","V")
set.seed(1234)
x <- rfast99(params = params, n = 200, q = q, q.arg = q.arg, rep = 20)

time <- c(0.25, 0.5, 1, 2, 4, 6, 8, 12, 24)
out <- solve_fun(x, model = FFPK, time = time, vars = "output")

# Check results of sensitivity measures
check(out)
plot(out)
heat_check(out, show.all = TRUE)
heat_check(out, index = "CI")
```
compile_model  

Model Compiler

Description

The compile_model is used to compile the model code that is written under C or GNU MCSim format and generate the executable program in numerical analysis.

Usage

```
code
compile_model(
  mName,  
  application = "mcsim",  
  use_model_file = TRUE,  
  mcsim_dir = NULL,  
  mod_dir = NULL)
```

Arguments

- `mName` a string giving the name of the model code (without extension).
- `application` a character to assign the specific methods (mcsim or R) that will be applied to the numerical analysis (default is mcsim). The version must be assigned for Windows user (default is 6.2.0).
- `use_model_file` a logical value to operate the compiler to model or C file, the default is set to TRUE to assign the GNU MCSim’s model file in compiling.
- `mcsim_dir` a character to assign the installed location of MCSim directory (The default is set to home).
- `mod_dir` a character giving the name of the directory that is used to store the model file.

Details

Generally, the solving function through GNU MCSim can provide faster computing speed than exporting C in R. Therefore, this function set use_model_file = TRUE and application = 'mcsim' as a default setting, suggesting to use GNU MCSim as main solver to solve the differential equation. To compile model code in Windows, be sure to install Rtools (rtools40) first. In addition, the version of GNU MCSim should provide to conduct model compiling in Windows.

Value

The default application is set to 'mcsim' to generate the executable program to solve differential equations by GNU MCSim. If application = 'R', the function will compile and create dynamic-link libraries (.dll) on Windows and shared objects (.so) on Unix-likes systems (e.g., Linux and MacOS) that can link with deSolve solver.
**mcsim_install**

### Description

Download the latest or specific version of **GNU MCSim** from the official website ([https://www.gnu.org/software/mcsim/](https://www.gnu.org/software/mcsim/)) and install it to the system directory.

### Usage

```r
mcsim_install(version = "6.2.0", install_dir = NULL, mxstep = 5000)

mcsim_version()

set_rtools40_path()
```

### Arguments

- **version**: a character of version number.
- **install_dir**: a character to assign the installed directory.
- **mxstep**: a numeric value to assign the maximum number of (internally defined) steps allowed during one call to the solver.

### Details

This function aims to help users download (source: https://ftp.gnu.org/gnu/mcsim/) and install **GNU MCSim** more easily. However, if you cannot install it through this function. The additional way is to follow the instruction and install it manually: [https://www.gnu.org/software/mcsim/mcsim.html#Installation](https://www.gnu.org/software/mcsim/mcsim.html#Installation)

The default `mxstp` is setting to 5000. The user can increase `mxstp` to avoid possible error return. If you meet any error when conduct sensitivity analysis, you can use this function to re-install **GNU MCSim** and set the higher `mxstp`. The default installed directory is under `/home/username` (Linux), `/Users/username` (MacOS), and `C:/Users/username/Documents` (windows). To install **GNU MCSim** in Windows, be sure to install Rtools first. The current suggested Rtools version is 4.0.

### Functions

- `mcsim_version()`: Return the version number.
- `set_rtools40_path()`: the function to set Rtools40 path

### References


[https://www.gnu.org/software/mcsim/](https://www.gnu.org/software/mcsim/)
Example PK Model for Sensitivity Analysis

Description

The example PK model that were used in sensitivity testing. Three examples are included: Flip-flop pharmacokinetic model, one-compartment toxicokinetic model from httk (Pearce et al. 2017), and acetaminophen pharmacokinetic model (Zurlinden et al. 2016).

Usage

FFPK(params, time, dose = 1)

pbtk1cpt_model()

pbpk_apap_model()

Arguments

- params: a numeric vector to define the input parameter value.
- time: a numeric vector to define the given time point(s).
- dose: a numeric value to define the given dose in flip-flop model.

Functions

- pbtk1cpt_model(): Download pbtk1cpt.model file.
- pbpk_apap_model(): Download pbpk_apap.model file.

References


Examples

```r
params <- c(F = 0.9, KA = 1.2, KE = 0.2, V = 1.5)
t <- seq(0, 12, 0.1)
C <- FFPK(params = params, time = t)
plot(t, C, type = "l", xlab = "time", ylab = "concentration")
```
Description

Create the PK profile of the output results based on the given parameter (uncertainty analysis). This function is used to visualize the corresponding output PK profile from the input parameters in sensitivity analysis. If there are multiple outputs in model, the generated result will be the first model variable (default). A PK plot is generated with median, 25%

Usage

\[ \text{pksim}(y, \text{vars} = 1, \log = F, \text{legend} = T, \ldots) \]

Arguments

- \textbf{y} a numeric array created from \texttt{solve_fun} or \texttt{solve_mcsim} function.
- \textbf{vars} a logical value or character to specific the display variable in simulation (default 1).
- \textbf{log} a logical value to transform the y-axis to log scale.
- \textbf{legend} a logical value to display the legend in the created plot.
- \ldots additional arguments to customize the graphical parameters.

\[ \text{rfast99} \]

Extended Fourier Amplitude Sensitivity Test with Random Phase Shift

Description

Applying the extended Fourier amplitude sensitivity Test algorithm to create the numeric sequences for each parameter (Saltelli et al. 1999). Each sequence is random generated based on the random phase shift approach. It is an extension based on the \texttt{fast99} function in \textit{sensitivity} package.

Usage

\[ \text{rfast99}( \text{params, n, M = 4, omega = NULL, q = NULL, q.arg = NULL, replicate = 5, conf = 0.95} ) \]
Arguments

params     an integer for the giving number of parameters, or a vector of character strings giving their names.
n         an integer for the sampling size.
M         an integer specifying the interference parameter. The default is 4.
omega     a vector giving the set of frequencies.
q         a vector of quantile functions names corresponding to wanted parameters distributions.
q.arg     a list of quantile functions parameters.
replicate an integer to define the number of replication. The default is 5.
conf      the confidence level for replication confidence intervals. The default is 0.95.

Value

The returned parameter value will be stored in an array with c(model evaluation, replication, parameters).

References


Examples

# Generate the parameter matrix with 20 replications
q <- "qunif"
q.arg <- list(min = 0, max = 1)

set.seed(1234)
x <- rfast99(params = 3, n = 100, replicate = 20, q = q, q.arg = q.arg)

## Not run:
save(x, file = "input_parameters.rda")

## End(Not run)
solve_fun

Solve PK Model Through deSolve Package or Analytical Function

Description

Solve time-dependent quantities/concentrations of different variables in PK model through the imported ode function in deSolve package. It can also be used to solve the function with analytical solution.

Usage

```r
solve_fun(
  x,
  time = NULL,
  initParmsfun = "initParms",
  initState,
  dllname = NULL,
  func = "derivs",
  initfunc = "initmod",
  outnames,
  method = "lsode",
  rtol = 1e-08,
  atol = 1e-12,
  model = NULL,
  lnparam = F,
  vars = NULL,
  tell = T,
  ...
)
```

Arguments

- `x` a list of storing information in the defined sensitivity function.
- `time` a vector to define the given time sequence.
- `initParmsfun` a character for the given specific initial parameter function.
- `initState` a vector that define the initial values of state variables for the ODE system.
- `dllname` a string giving the name of the shared library (without extension) that contains the compiled function.
- `func` the name of the function in the dynamically loaded shared library.
- `initfunc` the name of the initialization function (which initialises values of parameters), as provided in dllname.
- `outnames` the names of output variables calculated in the compiled function func.
- `method` method used by integrator (deSolve).
- `rtol` argument passed to integrator (deSolve).
solve_mcsim

atol  argument passed to integrator (deSolve).
model  the defined analytical equation with functional output.
lnparam  a logical value that make the statement of the log-transformed parameter (default FALSE).
vars  a character for the selected output.
tell  a logical value to automatically combine the result y to decoupling simulation x.
...  additional arguments for deSolve::ode method.

References


See Also

pksim

Examples

q <- "qunif"
q.arg <- list(list(min = 0.6, max = 1.0),
list(min = 0.5, max = 1.5),
list(min = 0.02, max = 0.3),
list(min = 20, max = 60))

params <- c("F","KA","KE","V")

set.seed(1234)
x <- rfast99(params = params, n = 200, q = q, q.arg = q.arg, rep = 20)

time <- seq(from = 0.25, to = 12.25, by = 0.5)
y <- solve_fun(x, model = FFPK, time = time, vars = "output")
pksim(y) # Visualize uncertainty of model output

solve_mcsim  Solve PK Model Through GNU MCSim

Description

Solve the differential equations of time-dependent quantity/concentration in different tissues/compartments through GNU MCSim.
solve_mcsim

Usage

```r
solve_mcsim(
  x,
  mName,
  infile.name = NULL,
  outfile.name = NULL,
  setpoint.name = NULL,
  params = NULL,
  vars = NULL,
  times = NULL,
  condition = NULL,
  generate.infile = T,
  tell = T,
  rtol = 1e-06,
  atol = 1e-06,
  monte_carlo = NULL,
  dist = NULL,
  q.arg = NULL,
  parallel = 1
)
```

generate_infile(
  mod = NULL,
  infile.name = NULL,
  outfile.name = NULL,
  params = NULL,
  vars,
  times,
  condition,
  rtol = 1e-06,
  atol = 1e-06,
  monte_carlo = NULL,
  dist = NULL,
  q.arg = NULL
)

Arguments

- `x` a list of storing information in the defined sensitivity function.
- `mName` a string giving the name of the model or C file (without extension).
- `infile.name` a character to assign the name of input file.
- `outfile.name` a character to assign the name of output file.
- `setpoint.name` a character to assign the name of file for parameter matrix.
- `params` a character to assign the testing parameters.
- `vars` a character or a vector to assign the selected output(s).
- `times` a numeric vector to define the given time point(s).
condition a character to set the specific parameter value in the input file.
generate.infile a logical value to automatically generate the input file.
tell a logical value to automatically combine the result y to decoupling simulation x.
rtol an argument passed to the integrator (default 1e-6).
atol an argument passed to the integrator (default 1e-6).
monte_carlo a numeric value to define the sample size in Monte Carlo simulation.
dist a vector of distribution names corresponding to <distribution-name> in GNU MCSim.
q.arg a list of shape parameters in the sampling distribution (dist).
parallel a numeric value to assign the number of cores in parallel computing (default is set to 1).
mod a list of model and parameters information that is used in solving differential equation.

Details
This function allows users to use external data file that assigned in setpoint.name as parameter matrix. If you want to use it, be sure to define n and setpoint.name.

Value
The output result is the 4-dimension array with c(model evaluations, replications, time-points, output variables).

Functions
• solve_mcsim(): Numerical analysis for the PK model by GNU MCSim.
• generate_infile(): Generate the GNU MCSim input file.

Examples

```r
## Not run:
pbtk1cpt_model()
mName <- "pbtk1cpt"
compile_model(mName)
q <- "qunif"
q.arg <- list(list(min = 0.4, max = 1.1),
              list(min = 0.1, max = 0.4),
              list(min = 1.0, max = 3.0))
params <- c("vdist", "ke", "kgutabs")
set.seed(1234)
x <- rfast99(params = params, n = 200, q = q, q.arg = q.arg, rep = 20)
```
tell2

```r
infile.name <- "example.in"
outfile.name <- "example.csv"
vars <- "Ccompartment"

t <- seq(from = 0.25, to = 12.25, by = 0.5)

y <- solve_mcsim(x, mName = mName, infile.name = infile.name,
                 setpoint.name = "setpoint.dat",
                 outfile.name = outfile.name, params = params, vars = vars, time = t,
                 condition = "Agutlument = 10")
pksim(y)

## End(Not run)
```

---

**tell2**

*The Decoupling Simulations*

**Description**

Integrate the decoupling simulations (parameter sequences) and estimation results to compute the sensitivity measures.

**Usage**

```r
tell2(x, y)
```

**Arguments**

- `x` a list of storing information in the defined sensitivity function.
- `y` a numeric array generated from the solutions of `solve_fun` or `solve_mcsim` function.

**Source**

This function is based on `tell` function in `sensitivity` package, which is an S3 generic method to estimate sensitivity measures by combining sensitivity object (`rfast99`) and external simulation results.
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