Package 'PKPDsim'

April 1, 2022

Type Package

Title Tools for Performing Pharmacokinetic-Pharmacodynamic Simulations

Version 1.1.1

Date 2022-03-31

Depends R (>= 3.0.2)

Imports Rcpp (>= 0.12.9), BH, data.table, stringr, MASS, randtoolbox, jsonlite, stats, parallel, magrittr

Suggests httr, testthat (>= 3.0.0), mockery

LinkingTo BH, Rcpp (>= 0.12.9)

Description Simulate dose regimens for pharmacokinetic-pharmacodynamic (PK-PD) models described by differential equation (DE) systems. Simulation using ADVAN-style analytical equations is also supported (Abuhelwa et al. (2015) <doi:10.1016/j.vascn.2015.03.004>).

License MIT + file LICENSE

LazyData TRUE

RoxygenNote 7.1.2

Config/testthat/edition 3

Encoding UTF-8

NeedsCompilation yes

Author Ron Keizer [aut, cre],
Jasmine Hughes [aut],
Dominic Tong [aut],
Kara Woo [aut],
InsightRX [cph, fnd]

Maintainer Ron Keizer <ron@insight-rx.com>

Repository CRAN

Date/Publication 2022-04-01 08:10:02 UTC

R topics documented:

PKPDsim-package *PKPDsim package*

Description

Simulate regimens for PKPD models defined by ODE systems

Author(s)

Ron Keizer <ronkeizer@gmail.com>

add_quotes *Put vector values in quotes*

Description

Put vector values in quotes

Usage

```
add_quotes(x, quote = "double")
```

Arguments

x	vector of string / numeric
quote	what type of quotes (‘double‘ or ‘single‘)

Value

Character vector of input with quotation marks around each value

add_ruv *Add residual variability to the dependent variable*

Description

Add residual variability to the dependent variable

Usage

```
add_ruv(x, ruv = list(), obs_type = 1)
```

Arguments

x	dependent value without residual variability
ruv	list specifying proportional, additive and/or exponential errors ('prop', 'add', 'exp')
obs_type	vector of observation types

Value

Input vector with residual variability added

---

add_ruv_to_quantile *Calculate the increase in a specific quantile for a distribution on y when residual variability is added*

Description

Calculate the increase in a specific quantile for a distribution on y when residual variability is added

Usage

```
add_ruv_to_quantile(y, sd_y, log_scale = FALSE, q = NULL, ruv = list(), ...)
```

Arguments

y	y with
sd_y	standard deviation of y without residual variability added. Will add normally distributed variability (potetially on log-scale).
log_scale	add variability on log scale (FALSE by default, DEPRECATED!).
q	quantile
ruv	list of residual variability ('prop' and 'add')
...	passed arguments

Value

Numeric vector of y values with residual variability

adherence_binomial *Binomial adherence*

Description

Model adherence as a binomial probability at the time of each occasion.

Usage

```
adherence_binomial(n = 100, prob)
```

Arguments

n	number of occasions
prob	binomial probability

Value

Returns a vector of length ‘n‘ containing values 0 (non-adherent) or 1 (adherent).

Numeric vector of length n

adherence_markov *Markov adherence model*

Description

Model adherence as a markov chain model, based on the probability of staying adherent and of becoming adherent once non-adherent. Assumes all patients start adherent.

Usage

```
adherence_markov(n = 100, p11 = 0.9, p01 = 0.7)
```

Arguments

n	number of occasions
p11	probability of staying adherent
p01	probability of going from non-adherent to adherent state

Value

Returns a vector of length ‘n‘ containing values 0 (non-adherent) or 1 (adherent).

Numeric vector of length n

advan *ADVAN-style functions to calculate linear PK systems*

Description

ADVAN-style functions to calculate linear PK systems

Usage

```
advan(model, cpp = TRUE)
```

Arguments

model	Standard linear PK model, e.g. 'pk_1cmt_iv_bolus'.
cpp	use C++-versions of model (~50x faster than R implementations)

Value

Model function

advan_create_data *Create ADVAN-style dataset*

Description

Create ADVAN-style dataset

Usage

```
advan_create_data(
  regimen,
  parameters,
  cmts = 5,
  t_obs = NULL,
  covariates = NULL,
  covariate_model = NULL
)
```

Arguments

regimen	PKPDsim regimen
parameters	list of parameters
cmts	number of compartments, minimum is 1. Default is 5, which is enough for most linear PK models. It is OK to have more compartments available than are actually being used.

t_obs	add observation timepoints to dataset
covariates	covariate list
covariate_model	covariate model equations, written in C

Value

Data frame of ADVAN-style data

`advan_parse_output` *Internal function to parse the raw output from ADVAN-style functions*

Description

Internal function to parse the raw output from ADVAN-style functions

Usage

```
advan_parse_output(data, cmts = 1, t_obs, extra_t_obs = TRUE, regimen)
```

Arguments

data	simulation output data
cmts	number of compartments
t_obs	observation times
extra_t_obs	leave extra added dose times in dataset?
regimen	PKPDsim regimen

Value

Data frame containing parsed simulation data

`advan_process_infusion_doses` *Add column RATEALL to ADVAN-style dataset to handle infusions*

Description

Function adapted from code from Abuhelwa, Foster, Upton JPET 2015. cleaned up and somewhat optimized. Can potentially be optimized more.

Usage

```
advan_process_infusion_doses(data)
```

Arguments

data	ADVAN-style dataset, e.g. created using ‘advan_create_data‘.

Value

Data frame containing additional RATEALL column.

References

Abuhelwa, A. Y., Foster, D. J. R., Upton, R. N. (2015) ADVAN-style analytical solutions for common pharmacokinetic models. J Pharmacol Toxicol Methods 73:42-8. DOI: 10.1016/j.vascn.2015.03.004

---

analytical_eqn_wrapper *Wrapper for using analytical equations with PKPD regimens*

Description

In development. Needs to be optimized significantly to be useful in production.

Usage

```
analytical_eqn_wrapper(analytical, design = NULL, parameters)
```

Arguments

analytical	analytical equation, taking parameters ‘amt‘, ‘parameters‘, and ‘t‘, and returning a vector of values for ‘y‘
design	design dataset created by ‘sim_ode‘
parameters	list of parameters

---

apply_lagtime *Apply lagtime to a regimen*

Description

Apply lagtime to a regimen

Usage

```
apply_lagtime(regimen, lagtime, parameters, cmt_mapping = NULL)
```

Arguments

regimen	PKPDsim regimen
lagtime	lagtime object, either single value / parameter name or vector of values/parameter names for all compartments.
parameters	parameter list, required if parameters are specified.
cmt_mapping	map of administration types to compartments, e.g. 'list("oral" = 1, "infusion" = 2, "bolus" = 2)'.

Value

Original regimen with lagtime added to dose times

---

bioavailability_to_R_code

Transforms bioavailability specs into appropriate R code

Description

Specialized wrapper around 'vector_to_R_code' that makes reasonable PK assumptions for when the bioavailability specification is NULL.

Usage

```
bioavailability_to_R_code(bioav)
```

Arguments

bioav	bioavailability specification, either NULL (assume a value of 1 in all compartments), a single value (assume it applies to all compartments), or a vector of values.

Value

character string of length 1

`calculate_parameters` *Calculate model-specific variables using a dummy call to sim_ode()*

Description

This is a convenience function for PKPDsim users, it is not used inside the 'sim_ode()" function in any way. This function is useful for converting from an estimated parameter to actual parameter, e.g. when clearance is specified as 'CLi = CL * (WT/70) * (1/CR)' it can be used to calculate 'CLi' without having to write that function a second time in R.

Usage

```
calculate_parameters(
  ode = NULL,
  parameters = NULL,
  covariates = NULL,
  include_parameters = TRUE,
  include_variables = TRUE,
  ...
)
```

Arguments

`ode`	PKPDsim model object
`parameters`	parameter list
`covariates`	covariate list. Make sure to include covariates at the right time point, since only last observed covariate values are used.
`include_parameters`	boolean, include parameters?
`include_variables`	boolean, include variables?
`...`	arguments to pass on to simulation function

Value

List of model-specific variables

calc_dydP — *Calculate derivative*

Description

Calculate derivative

Usage

```
calc_dydP(dy, y, rel_delta, log_y)
```

Arguments

dy	dy
y	dependent value
rel_delta	relative delta
log_y	logical indicating if the dependent variable is log transformed

calc_ss_analytic — *Returns the state of a linear PK system at steady state (trough) using analytics equations (so for linear PK systems only).*

Description

Basically it performs a PK simulation using analytic equations instead of ODEs to steady state (n=45 days, increased if needed).

Usage

```
calc_ss_analytic(
  f = "1cmt_oral",
  dose,
  interval,
  t_inf = NULL,
  model,
  parameters,
  covariates = NULL,
  map = NULL,
  n_days = 45,
  n_transit_compartments = 0,
  auc = FALSE
)
```

Arguments

f	analytic equation to use, must be one of ‘names(advan_funcs)‘
dose	dose
interval	interval
t_inf	infusion time
model	PKPDsim model
parameters	parameters list
covariates	covariates list
map	list for remapping parameters, ex: ‘list(CL = "CL", V = "V")‘
n_days	number of days at which to assume steady state. Default is 45.
n_transit_compartments	number of transit compartments, will insert n compartments between the first (dose) compartment and the second (central) compartment.
auc	add (empty) AUC compartment at end of state vector?

Details

It can also be used for models with transit compartments, however, the assumption is made that at the end of the dosing interval the amount in the transit compartments is negligible (0).

Value

State vector of a linear pharmacokinetic system at steady state

---

check_iov_specification

Checks that IOV was specified appropriately

Description

Inter-occasion variability (IOV) is expected to be supplied as a list with ‘cv‘ and ‘n_bins‘ specified. ‘cv‘ is expected to be a named list with IOV for each PK parameter. This function then checks to ensure that the PK code or ODE code contains an IOV term for each PK parameter specified.

Usage

```
check_iov_specification(iov, code, pk_code)
```

Arguments

iov	IOV specifications, provided as a nested named list.
code	C++ ODE code, supplied as a string
pk_code	C++ PK code, supplied as a string

check_mixture_model *Check that mixture model is specified in right format and within constraints (1 parameter, 2 groups)*

Description

Check that mixture model is specified in right format and within constraints (1 parameter, 2 groups)

Usage

```
check_mixture_model(mixture, parameters)
```

Arguments

mixture	mixture model specification (as list, e.g. 'list("CL" = list(values=c(5, 10), probability=0.3))')
parameters	vector of parameter names

compile_sim_cpp *Compile ODE model to c++ function*

Description

Compile ODE model to c++ function

Usage

```
compile_sim_cpp(
  code,
  dose_code,
  pk_code,
  size,
  p,
  cpp_show_code,
  code_init = NULL,
  state_init = NULL,
  declare_variables = NULL,
  variables = NULL,
  covariates = NULL,
  obs = NULL,
  dose = NULL,
  iov = NULL,
  compile = TRUE,
  verbose = FALSE,
  as_is = FALSE
)
```

Arguments

code	C++ code ODE system
dose_code	C++ code per dose event
pk_code	C++ code per any event (similar to $PK)
size	size of ODE system
p	parameters (list)
cpp_show_code	show output c++ function?
code_init	code for initialization of state
state_init	state init vector
declare_variables	variable declaration for all required variables (including user-specified)
variables	only the user-specified variables
covariates	covariates specification
obs	observation specification
dose	dose specification
iov	iov specification
compile	compile or not?
verbose	show more output
as_is	use C-code as-is, don't substitute line-endings or shift indices

Value

List containing ODE definition in C++ code and simulation function

---

covariates_table_to_list

Convert covariate table specified as data.frame

Description

Can handle time-varying data too, if 't' or 'time' is specified as column

Usage

```
covariates_table_to_list(covariates_table, covariates_implementation = list())
```

Arguments

covariates_table	'data.frame" with covariates in columns. Potentially with 'id' and 't' columns
covariates_implementation	'list' with implementation method per covariate

Value

List of covariates

covariate_last_obs_only *Use only last observed covariate values*

Description

Use only last observed covariate values

Usage

```
covariate_last_obs_only(covariates)
```

Arguments

covariates	covariates object

Value

List containing same elements as input covariate object but including only the last value for each covariate

create_event_table *Create an event table*

Description

Create an event table

Usage

```
create_event_table(
  regimen,
  t_max = NULL,
  t_obs = NULL,
  t_tte = NULL,
  t_init = 0,
  p,
  covariates,
  model = NULL,
  obs_type = NULL
)
```

Arguments

regimen	regimen
t_max	t_max
t_obs	t_obs
t_tte	t_tte
t_init	t_init
p	parameters
covariates	covariates
model	model
obs_type	observation type

---

create_obs_data *Create obs data*

Description

Used by sim() to arrange data from ode() function into the correct format.

Usage

```
create_obs_data(ode_data, obs_attr, id)
```

Arguments

ode_data	data frame of output from ode() function
obs_attr	"obs" attribute from ode() function
id	ID of the individual

See Also

sim()

cv_to_omega *Create lower-diagonal omega matrix from CV for parameter estimates*

Description

Create lower-diagonal omega matrix from CV for parameter estimates

Usage

```
cv_to_omega(par_cv = NULL, parameters = NULL)
```

Arguments

par_cv	list of parameter CVs
parameters	list of parameters

Value

a vector describing the lower triangle of the omega (between-subject variability) matrix

See Also

sim_ode

define_tdm_init_model *defines C code for TDM before dose conditions*

Description

Currently only available for 1-cmt and 2-cmt IV models

Usage

```
define_tdm_init_model(def)
```

Arguments

def	model definition, named recursive list with at least the objects ‘misc$model_type‘, ‘parameters‘ and ‘variables‘

Value

model defintion with ‘state_init‘ object added describing how to initializing the compartments.

detect_ode_syntax *Auto-detect the syntax for the ODE code*

Description

Either PKPDsim or RxODE

Usage

```
detect_ode_syntax(code)
```

Arguments

code	character string with ODE code

Value

List with elements `from` and `to` indicating the syntax for the ODE code

f_cov *covariate function builder*

Description

covariate function builder

Usage

```
f_cov(...)
```

Arguments

...	parameters to pass to cov

Value

Covariate function

get_ode_model_size *Get the number of states in the ODE from the code code C++ code for model*

Description

Get the number of states in the ODE from the code code C++ code for model

Usage

```
get_ode_model_size(code)
```

Arguments

code	C++ code

Value

Number of states in the ODE model

get_parameters_from_code *Get model parameters from code*

Description

Get model parameters from code

Usage

```
get_parameters_from_code(code, state_init, declare_variables = NULL)
```

Arguments

code	code
state_init	state init vector
declare_variables	declared variables

Value

Vector of parameter names

`get_t_obs_from_regimen` *Extract sensible default observation times from a specified regimen*

Description

Extract sensible default observation times from a specified regimen

Usage

```
get_t_obs_from_regimen(
  regimen = NULL,
  obs_step_size = NULL,
  t_max = NULL,
  covariates = NULL,
  extra_t_obs = NULL,
  t_init = 0
)
```

Arguments

`regimen`	regimen created using 'new_regimen()'
`obs_step_size`	step size between observations. Will be auto-calculated if NULL
`t_max`	max time value
`covariates`	covariates object, created using 'list(new_covariate(), ...)'
`extra_t_obs`	add timepoints to t_obs at which covariate is changing ('T'/'F')
`t_init`	time of initization of the ODE system. Usually 0.

`get_var_y` *Get expected variance/sd/ci of dependent variable based on PKPDsim model, parameters, and regimen*

Description

Get expected variance/sd/ci of dependent variable based on PKPDsim model, parameters, and regimen

Usage

```
get_var_y(
  model = NULL,
  parameters = list(),
  regimen = list(),
  t_obs = c(1:48),
  obs_comp = NULL,
  obs_variable = NULL,
  omega = c(0.1, 0.05, 0.1),
  omega_full = NULL,
  n_ind = NULL,
  ruv = NULL,
  y = NULL,
  rel_delta = 1e-04,
  method = "delta",
  sequence = NULL,
  auc = FALSE,
  sd = TRUE,
  q = NULL,
  in_parallel = FALSE,
  n_cores = 3,
  return_all = FALSE,
  ...
)
```

Arguments

model	model, created using 'PKPDsim::new_ode_model()'
parameters	parameters list
regimen	regimen, as created using 'PKPDsim::new_regimen()'
t_obs	vector of observation times
obs_comp	observation compartment. If NULL will be "obs" (default)
obs_variable	observation variable. If NULL, will be ignored, otherwise will override 'obs_comp'.
omega	triangle omega block
omega_full	full omega block
n_ind	number of individuals to simulate with sim method
ruv	residual variability, supplied as a named list, ex: 'list(prop = 0, add = 0, exp = 0)'
y	vector of observations. If NULL, then a new simulation will be performed.
rel_delta	rel_delta
method	method, 'delta' or 'sim'
sequence	for simulations, if not NULL the pseudo-random sequence to use, e.g. "halton" or "sobol". See 'mvrnorm2' for more details.
auc	is AUC?

sd	return as standard deviation ('TRUE') or variance ('FALSE')
q	return vector of quantiles instead of sd/var. Will return parametric quantiles when deltamethod is used, non-parametric for simulation-basesd methods.
in_parallel	run simulations in parallel?
n_cores	if run in parallel, on how many cores?
return_all	return object with all relevant information?
...	passed on to 'sim_ode()'

Value

Vector of standard deviations or variances (or quantiles thereof) for dependent value variable

---

ifelse0 *ifelse function but then based on whether value is NULL or not*

Description

ifelse function but then based on whether value is NULL or not

Usage

```
ifelse0(value = NULL, alternative = NULL, allow_null = FALSE)
```

Arguments

value	metadata list object
alternative	alternative value
allow_null	can the alternative be NULL?

Value

value if non-NULL; alternative otherwise

is_newer_package *Check if package number is different from currently installed, and provide some messaging.*

Description

Technically it only checks if a package version is different, not necessarily a higher version number.

Usage

```
is_newer_package(package, new_version)
```

Arguments

package	R package
new_version	new version number

is_positive_definite *Is matrix positive definite*

Description

Is matrix positive definite

Usage

```
is_positive_definite(x)
```

Arguments

x	matrix, specified either as vector of lower triangle, or full matrix (as matrix class)

Value

TRUE if x is positive definite; FALSE otherwise.

`join_cov_and_par` *Combines covariates and parameters into a single list, useful for reparametrization of the model.*

Description

Combines covariates and parameters into a single list, useful for reparametrization of the model.

Usage

```
join_cov_and_par(covs, pars)
```

Arguments

`covs`	covariates object
`pars`	model parameters, such as the output of the ‘parameters()‘ call frmo a model library.

Value

List containing covariates and parameters

`join_regimen` *Join two dosing regimens*

Description

Join two dosing regimens

Usage

```
join_regimen(
  regimen1 = NULL,
  regimen2 = NULL,
  interval = NULL,
  dose_update = NULL,
  t_dose_update = NULL,
  continuous = FALSE
)
```

Arguments

regimen1	first regimen
regimen2	second regimen
interval	interval between regimen1 and regimen2 (if dose_update not specified)
dose_update	dose number at which to override regimen1 with regimen 2 (if interval not specified)
t_dose_update	dose time from which to update regimen
continuous	for joining continuous infusions

Value

Joined regimen

---

merge_regimen *Merge two regimens together.*

Description

In contrast to 'join_regimen', which joins two consecutive regimens together, 'merge_regimen' merges two or more regimens given at the same time. This can e.g. be used to define regimens for multi-drug models.

Usage

```
merge_regimen(regimens)
```

Arguments

regimens	List of PKPDsim regimens created with 'new_regimen'.

Value

Merged regimens

`model_from_api` *Load model definition from API, and compile to R library*

Description

Load model definition from API, and compile to R library

Usage

```
model_from_api(
  url,
  model = NULL,
  nonmem = NULL,
  verbose = TRUE,
  get_definition = FALSE,
  to_package = FALSE,
  force = FALSE,
  install_all = FALSE,
  ...
)
```

Arguments

`url`	URL or file path to JSON representation of model
`model`	model id (used in messages)
`nonmem`	URL or file path to NONMEM file
`verbose`	verbosity (T/F)
`get_definition`	return only the model definition, do not compile
`to_package`	compile to package?
`force`	force install even if same version number of model already installed.
`install_all`	force install all, even if model inactive
`...`	arguments passed to `new_ode_model()` function

Value

Model object created with `new_ode_model()`

model_library *Model library*

Description

Model library

Usage

```
model_library(name = NULL)
```

Arguments

name	name of model in library. If none specified, will show list of available models.

Value

List containing information about the named model

mvrnorm2 *More powerful multivariate normal sampling function*

Description

Besides standard multivariate normal sampling (mvrnorm), allows exponential multivarate normal and quasi-random multivariate normal (using the randtoolbox) all using the same interface.

Usage

```
mvrnorm2(n, mu, Sigma, exponential = FALSE, sequence = NULL, ...)
```

Arguments

n	number of samples
mu	mean
Sigma	covariance matrix
exponential	exponential distribution (i.e. multiply mu by exponential of sampled numbers)
sequence	any sequence available in the randtoolbox, e.g. 'halton', or 'sobol'
...	parameters passed to mvrnorm or randtoolbox sequence generator

Value

Multivariate normal samples

na_locf *Fill in NAs with the previous non-missing value*

Description

Inspired by zoo::na.locf0

Usage

```
na_locf(object, fromLast = FALSE)
```

Arguments

object	an object
fromLast	logical. Causes observations to be carried backward rather than forward. Default is FALSE.

Value

Original object with NAs filled in

new_adherence *Probabilistically model adherence*

Description

Model the drug adherence using either a binomial probability distribution or a markov chain model based on the probability of staying adherent and of becoming adherent once non-adherent.

Usage

```
new_adherence(
  n = 100,
  type = c("markov", "binomial"),
  p_markov_remain_ad = 0.75,
  p_markov_become_ad = 0.75,
  p_binom = 0.7
)
```

Arguments

n	number of occasions to simulate
type	type of adherence simulation, either "markov" or "binomial"
p_markov_remain_ad	markov probability of staying adherent
p_markov_become_ad	markov probability of going from non-adherent to adherent state
p_binom	binomial probability of being adherent

Value

Returns a vector of length ‘n‘ containing values 0 (non-adherent) or 1 (adherent).

Numeric vector of length n

---

new_covariate *New covariate*

Description

Describe data for a covariate, either fixed or time-variant

Usage

```
new_covariate(
  value = NULL,
  times = NULL,
  implementation = "interpolate",
  unit = NULL,
  interpolation_join_limit = 1,
  remove_negative_times = TRUE,
  comments = NULL,
  verbose = TRUE
)
```

Arguments

value	a numeric vector
times	NULL for time-invariant covariate or a numeric vector specifying the update times for the covariate
implementation	for time-varying covariates either 'LOCF' (last observation carried forward) or 'interpolate' (default)
unit	specify covariate unit (optional, for documentation purposes only)

`interpolation_join_limit`
: for `interpolate` option, if covariate timepoints are spaced too close together, the ODE solver sometimes chokes. This argument sets a lower limit on the space between timepoints. It will create average values on joint timepoints instead. If undesired set to NULL or 0.

`remove_negative_times`
: TRUE`` or FALSE‘

`comments`
: `NULL`, or vector of length equal to `value` specifying comments to each observation

`verbose`
: verbosity

Value

Object of class `"covariate"`

`new_covariate_model` *covariate model function*

Description

covariate model function

Usage

```
new_covariate_model(model = list())
```

Arguments

`model`
: covariate model specified as list

Value

List containing model function(s)

`new_ode_model` *Create new ODE model*

Description

Create new ODE model

Usage

```
new_ode_model(
  model = NULL,
  code = NULL,
  pk_code = NULL,
  dose_code = NULL,
  file = NULL,
  func = NULL,
  state_init = NULL,
  parameters = NULL,
  reparametrization = NULL,
  mixture = NULL,
  units = NULL,
  size = NULL,
  lagtime = NULL,
  obs = list(cmt = 1, scale = 1),
  dose = list(cmt = 1),
  covariates = NULL,
  declare_variables = NULL,
  iiv = NULL,
  iov = NULL,
  omega_matrix = NULL,
  ruv = NULL,
  ltbs = NULL,
  misc = NULL,
  cmt_mapping = NULL,
  int_step_size = NULL,
  default_parameters = NULL,
  fixed = NULL,
  cpp_show_code = FALSE,
  package = NULL,
  test_file = NULL,
  install = TRUE,
  folder = NULL,
  lib_location = NULL,
  verbose = FALSE,
  as_is = FALSE,
  nonmem = NULL,
  comments = NULL,
  version = "0.1.0",
  quiet = ""
)
```

Arguments

model	model name from model library
code	C++ code specifying ODE system
pk_code	C++ code called at any event

dose_code	C++ code called at dose event only
file	file containing C++ code
func	R function to be used with deSolve library
state_init	vector of state init
parameters	list or vector of parameter values
reparametrization	list of parameters with definitions that reparametrize the linear PK model to a 1-, 2- o4 3-compartment PK with standardized parametrization.
mixture	for mixture models, provide a list of the parameter associated with the mixture and it's possible values and probabilities (of the first value), e.g. 'list(CL = list(value = c(10, 20), probability = 0.3)'.
units	list or vector of parameter units
size	size of state vector for model. Size will be extracted automatically from supplied code, use this argument to override.
lagtime	lag time
obs	list with "scale": character string with definition for scale, e.g. "V" or "V*(WT/70)". If NULL, scale defaults to 1., and "cmt" the observation compartment
dose	specify default dose compartment, e.g. list(cmt = 1)
covariates	specify covariates, either as a character vector or a list. if specified as list, it allows use of timevarying covariates (see 'new_covariate()' function for more info)
declare_variables	declare variables
iiv	inter-individual variability, can optionally be added to library
iov	inter-occasion variability, can optionally be added to library
omega_matrix	variance-covariance matrix for inter-individual variability, can optionally be added to library
ruv	residual variability, can optionally be added to library
ltbs	log-transform both sides. Not used in simulations, only for fitting (sets attribute 'ltbs').
misc	a list of miscellaneous model metadata
cmt_mapping	list indicating which administration routes apply to which compartments. Example: 'list("oral" = 1, "infusion" = 2)'
int_step_size	step size for integrator. Can be pre-specified for model, to override default for 'sim_ode()'
default_parameters	population or specific patient values, can optionally be added to library
fixed	parameters that should not have iiv added.
cpp_show_code	show generated C++ code
package	package name when saving as package
test_file	optional test file to be included with package

install	install package after compilation?
folder	base folder name to create package in
lib_location	install into folder (‘–library‘ argument)
verbose	show more output
as_is	use C-code as-is, don’t substitute line-endings or shift indices
nonmem	add nonmem code as attribute to model object
comments	comments for model
version	number of library
quiet	passed on to ‘system2‘ as setting for stderr and stdout; how to output cmd line output. Default (‘""‘) is R console, NULL or FALSE discards. TRUE captures the output and saves as a file.

Value

If package name is NULL, returns the model object. Otherwise has no return value.

---

new_regimen *Dose regimen for sim_ode*

Description

Create a dosing regimen for use with sim_ode

Usage

```
new_regimen(
  amt = 100,
  interval = NULL,
  n = 3,
  times = NULL,
  type = NULL,
  t_inf = NULL,
  rate = NULL,
  t_lag = NULL,
  cmt = NULL,
  checks = TRUE,
  ss = FALSE,
  n_ss = NULL,
  first_dose_time = now_utc()
)
```

Arguments

amt	dosing amount, either a single value (which will repeated for multiple doses), or a vector with doses for each administration
interval	dosing interval (requires n as argument)
n	number of doses (requires interval as argument)
times	vector describing dosing times. Overrides specified times using interval and n arguments
type	either "infusion", "oral" or "bolus".
t_inf	infusion time (if 'type'=='infusion')
rate	infusion rate (if 'type'=='infusion'). 'NULL' by default. If specified, overrides 't_inf'
t_lag	lag time (can be applied to any dose type, not only oral). Will just be added to 'times'
cmt	vector of dosing compartments (optional, if NULL will dosing compartment defined in model will be used)
checks	input checks. Remove to increase speed (e.g. for population-level estimation or optimal design)
ss	steady state? boolean value whether to simulate out to steady state first (steady state will be based on specified 'amt' and 'interval', 'times' will be ignored).
n_ss	how many doses to simulate before assumed steady state. Default is 4 * 24 / 'interval'.
first_dose_time	datetime stamp of first dose (of class 'POSIXct'). Default is current date time.

Value

a list containing calculated VPC information, and a ggplot2 object

See Also

sim_ode

Examples

```
r1 <- new_regimen(amt=50, interval=12, n=20) # dose 50mg, q12hrs for 10 days
r2 <- new_regimen(amt=50, times=c(0:19)*12)  # same, but using explicit times
r3 <- new_regimen(amt=c(rep(100,4), rep(50,16)), times=c(0:19)*12) # first 4 doses higher dose
```

`nlmixr_parse_parameters` *Function to parse parameters for a model into a structure used by nlmixr*

Description

Function to parse parameters for a model into a structure used by nlmixr

Usage

```
nlmixr_parse_parameters(
  parameters = list(CL = 5, V = 50),
  omega = c(0.1, 0.05, 0.1),
  res_var = list(prop = 0.1, add = 1),
  fixed = c(),
  log_transform = TRUE,
  ...
)
```

Arguments

`parameters`	list of parameters
`omega`	vector describing the lower-diagonal of the between-subject variability matrix
`res_var`	residual variability. Expected a list with arguments 'prop', 'add', and/or 'exp'. NULL by default.
`fixed`	vector of fixed parameters
`log_transform`	log-transform estimated parameters in nlmixr?
`...`	passed on

Value

List of parameters that can be used by nlmixr

`nm_to_regimen` *Create a regimen from NONMEM data*

Description

Create a regimen based on a NONMEM, or NONMEM-like dataset

Usage

```
nm_to_regimen(data, reset_time = TRUE, first_only = FALSE)
```

Arguments

data	NONMEM-type dataset
reset_time	start time for each simulated patient at 0, irrespective of design in dataset
first_only	use only design from first individual in dataset

Value

Regimen object

---

now_utc *Current time in UTC*

Description

Current time in UTC

Usage

```
now_utc()
```

Value

POSIXct object containing current time in UTC

OneCompIVbolus *ADVAN-style equations*

Description

Adapted from Abuhelwa et al. JPET 2015

Usage

```
OneCompIVbolus(d)
```

Arguments

d	data, a NONMEM style data frame for 1 subject with columns for TIME, AMT, MDV, DV, CL, V

Details

Functions for calculating drug amount in each compartments of the common pharmacokinetic models (1,2,3 compartment IV bolus, IV infusion, and first-order absorption models)

Definitions: - A*last: is the initial amount at the beginning of each time interval (t, t=t2-t1) of a corresponding compartment (i.e. drug amount at the end of the last time interval) - E* : the sum of Exit (elimination) rate constant of the corresponding compartment. IV bolus- 1 compartment

Value

Returns a dataframe with populated columns for A1, and DV

References

Abuhelwa, A. Y., Foster, D. J. R., Upton, R. N. (2015) ADVAN-style analytical solutions for common pharmacokinetic models. J Pharmacol Toxicol Methods 73:42-8. DOI: 10.1016/j.vascn.2015.03.004

OneCompIVinfusion *IV infusion- 1 compartment*

Description

IV infusion- 1 compartment

Usage

```
OneCompIVinfusion(d)
```

Arguments

d	data, accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV, RATE, RATEALL, DV, CL, V

Value

Returns a dataframe with populated columns for A1, and DV

OneCompOral *first-order absorption 1 compartment*

Description

first-order absorption 1 compartment

Usage

```
OneCompOral(d)
```

Arguments

d	data, accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV,DV, CL, V, KA & F1

Value

Returns a dataframe with populated columns for A1, A2 and DV

parse_obs_types *Parse observation types to simulation code*

Description

Parse observation types to simulation code

Usage

```
parse_obs_types(obs)
```

Arguments

obs	specified observation object including at least a description of which variable(s) are associated with a particular compartment, e.g. 'list(variable="CONC", scale="1")'.

pkdata *PK dataset*

Description

Example PK dataset

Usage

```
pkdata
```

Format

A data frame with 624 rows and 12 variables in NONMEM format

pkpdsim_to_nlmixr *Convert a model generated with PKPDsim to an object for nlmixr*

Description

Convert a model generated with PKPDsim to an object for nlmixr

Usage

```
pkpdsim_to_nlmixr(
  model = NULL,
  parameters = NULL,
  omega = NULL,
  res_var = NULL,
  fixed = c(),
  ini_code = NULL,
  model_code = NULL,
  model_par_code = NULL,
  verbose = FALSE,
  ...
)
```

Arguments

model	PKPDsim model
parameters	list of parameters
omega	vector describing the lower-diagonal of the between-subject variability matrix
res_var	residual variability. Expected a list with arguments 'prop', 'add', and/or 'exp'. NULL by default.
fixed	vector of fixed (not estimated) parameter names
ini_code	manually specify the 'ini' block for nlmixr
model_code	manually specify the 'model' block for nlmixr
model_par_code	manually specify the parameters section inside the 'model' block for nlmixr
verbose	verbose, 'TRUE' or 'FALSE'
...	passed on

Value

nlmixr function

---

pop_regimen *Remove n doses (from tail) of PKPDsim regimen*

Description

Opposite of shift_regimen()

Usage

```
pop_regimen(regimen, n = 1)
```

Arguments

regimen	PKPDsim regimen created using ‘new_regimen()‘
n	number of doses to pop from regimen

Value

Input regiment minus selected number of doses

See Also

shift_regimen

---

print.covariate *Print function for PKPDsim covariate object*

Description

Print function for PKPDsim covariate object

Usage

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

Arguments

x	covariate object
...	additional arguments

Value

No return value, print function.

---

print.PKPDsim *Print function for PKPDsim simulation function*

Description

Print function for PKPDsim simulation function

Usage

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

Arguments

x	function
...	additional arguments

Value

No return value, print function.

---

print.regimen *Print function for PKPDsim regimen*

Description

Print function for PKPDsim regimen

Usage

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

Arguments

x	regimen
...	arguments to pass

Value

No return value, print function.

---

print_list *Return a list in R syntax*

Description

Return a list in R syntax

Usage

```
print_list(x, wrapper = TRUE, quote = FALSE)
```

Arguments

x	list to be printed
wrapper	wrap in list object?
quote	add quotes to values in list definition?

Value

Original list in R syntax

`read_model_json` *Read model definition from JSON*

Description

Does some substitution of escaped characters in strings in the JSON file, then converts to a list with `jsonlite::fromJSON()`

Usage

```
read_model_json(path)
```

Arguments

`path`	Path to JSON file

Value

List containing contents of original JSON file

`regimen_to_nm` *Convert PKPDsim regimen to NONMEM table (doses only)*

Description

Convert PKPDsim regimen to NONMEM table (doses only)

Usage

```
regimen_to_nm(reg = NULL, dose_cmt = 1, n_ind = 1, t_obs = NULL, obs_cmt = 1)
```

Arguments

`reg`	'PKPDsim' regimen, created using 'new_regimen()' function
`dose_cmt`	dosing compartment, if not specified in 'reg' object
`n_ind`	repeat for 'n_ind' subjects
`t_obs`	add observation time(s)
`obs_cmt`	observation compartment for added observation time(s)

Value

Data frame containing doses

`reparametrize` *Reparametrize model parameters using a reparametrization defined within the model.*

Description

Mostly useful for reparametrizing models into standard parametrizations, e.g. to NONMEM TRANS or clinPK parametrizations.

Usage

```
reparametrize(model, parameters, covariates)
```

Arguments

`model`	PKPDsim model, compiled using 'reparametrization' argument or in metadata object.
`parameters`	list of model parameters
`covariates`	covariates list, specified as PKPDsim covariates

Value

Reparameterized model parameters

`search_replace_in_file` *Find string and replace in file*

Description

Find string and replace in file

Usage

```
search_replace_in_file(files = c(), find = NULL, replacement = NULL)
```

Arguments

`files`	vector of files
`find`	find what string, vector of character
`replacement`	replace with what, vector of character, should be equal in lenght to 'find'

Value

Function does not return a value but edits files on disk

`shift_regimen` *Remove n doses (from start) of PKPDsim regimen*

Description

Opposite of pop_regimen()

Usage

```
shift_regimen(regimen, n = 1, reset_time = TRUE)
```

Arguments

`regimen`	PKPDsim regimen created using 'new_regimen()'
`n`	number of doses to shift regimen
`reset_time`	reset the remaining doses to start at t=0?

Value

Regimen with selected number of doses removed from start

See Also

pop_regimen

`shift_state_indices` *R starts counting vector indices at 1, c++ starts at 0, so reduce all state numbers in the Cpp function definition by 1*

Description

R starts counting vector indices at 1, c++ starts at 0, so reduce all state numbers in the Cpp function definition by 1

Usage

```
shift_state_indices(ode_def, n = -1)
```

Arguments

`ode_def`	ODE definition
`n`	add/substract what number, default = -1

`sim` *Simulate ODE or analytical equation*

Description

Simulates a specified regimen using ODE system or analytical equation

Usage

```
sim(
  ode = NULL,
  analytical = NULL,
  parameters = NULL,
  parameters_table = NULL,
  mixture_group = NULL,
  omega = NULL,
  omega_type = "exponential",
  res_var = NULL,
  iov_bins = NULL,
  seed = NULL,
  sequence = NULL,
  n_ind = 1,
  event_table = NULL,
  regimen = NULL,
  lagtime = NULL,
  covariates = NULL,
  covariates_table = NULL,
  covariates_implementation = list(),
  covariate_model = NULL,
  A_init = NULL,
  only_obs = FALSE,
  obs_step_size = NULL,
  int_step_size = 0.01,
  t_max = NULL,
  t_obs = NULL,
  t_tte = NULL,
  t_init = 0,
  obs_type = NULL,
  duplicate_t_obs = FALSE,
  extra_t_obs = TRUE,
  rtte = FALSE,
  checks = TRUE,
  verbose = FALSE,
  return_event_table = FALSE,
  return_design = FALSE,
  output_include = list(parameters = FALSE, covariates = FALSE),
  ...
```

)

Arguments

ode	function describing the ODE system
analytical	string specifying analytical equation model to use (similar to ADVAN1-5 in NONMEM). If specified, will not use ODEs.
parameters	model parameters
parameters_table	dataframe of parameters (with parameters as columns) containing parameter estimates for individuals to simulate. Formats accepted: data.frame, data.table, or list of lists.
mixture_group	mixture group for models containing mixtures. Should be either '1' or '2', since only two groups are currently allowed.
omega	vector describing the lower-diagonal of the between-subject variability matrix
omega_type	exponential or normal, specified as vector
res_var	residual variability. Expected a list with arguments 'prop', 'add', and/or 'exp'. NULL by default.
iov_bins	allow override of the default IOV bins for a model. Specified as a vector of timepoints specifying the bin separators, e.g. 'iov_bins = c(0, 24, 48, 72, 9999)'.
seed	set seed for reproducible results
sequence	if not NULL specifies the pseudo-random sequence to use, e.g. "halton" or "sobol". See 'mvrnorm2' for more details.
n_ind	number of individuals to simulate
event_table	use a previously created 'design' object used for ODE simulation instead of calling create_event_table() to create a new one. Especially useful for repeated calling of sim(), such as in optimizations or optimal design analysis. Also see 'sim_core()' for even faster simulations using precalculated 'design' objects.
regimen	a regimen object created using the regimen() function
lagtime	either a value (numeric) or a parameter (character) or NULL.
covariates	list of covariates (for single individual) created using 'new_covariate()' function
covariates_table	data.frame (or unnamed list of named lists per individual) with covariate values
covariates_implementation	used only for 'covariates_table', a named list of covariate implementation methods per covariate, e.g. 'list(WT = "interpolate", BIN = "locf")'
covariate_model	R code used to pre-calculate effective parameters for use in ADVAN-style analytical equations. Not used in ODE simulations.
A_init	vector with the initial state of the ODE system
only_obs	only return the observations
obs_step_size	the step size between the observations

int_step_size	the step size for the numerical integrator
t_max	maximum simulation time, if not specified will pick the end of the regimen as maximum
t_obs	vector of observation times, only output these values (only used when t_obs==NULL)
t_tte	vector of observation times for time-to-event simulation
t_init	initialization time before first dose, default 0.
obs_type	vector of observation types. Only valid in combination with equal length vector 't_obs'.
duplicate_t_obs	allow duplicate t_obs in output? E.g. for optimal design calculations when t_obs = c(0,1,2,2,3). Default is FALSE.
extra_t_obs	include extra t_obs in output for bolus doses? This is only activated when 't_obs' is not specified manually. E.g. for a bolus dose at t=24, if FALSE, PKPDsim will output only the trough, so for bolus doses you might want to switch this setting to TRUE. When set to "auto" (default), it will be TRUE by default, but will switch to FALSE whenever 't_obs' is specified manually.
rtte	should repeated events be allowed (FALSE by default)
checks	perform input checks? Default is TRUE. For calculations where sim_ode is invoked many times (e.g. population estimation, optimal design) it makes sense to switch this to FALSE (after confirming the input is correct) to improve speed.
verbose	show more output
return_event_table	return the event table for the simulation only, does not run the actual simulation. Useful for iterative use of sim().
return_design	returns the design (event table and several other details) for the simulation, does not run the actual simulation. Useful for iterative functions like estimation in combination with 'sim_core()', e.g. for estimation and optimal design.
output_include	list specyfing what to include in output table, with keys 'parameters' and 'covariates'. Both are FALSE by default.
...	extra parameters

Value

a data frame of compartments with associated concentrations at requested times

Simulated regimen

See Also

sim_ode_shiny

Examples

```
p <- list(
  CL = 38.48,
```

```
  V  = 7.4,
  Q  = 7.844,
  V2 = 5.19,
  Q2  = 9.324,
  V3 = 111
)

omega <- c(0.3,       # IIV CL
           0.1, 0.3)  # IIV V

r1 <- new_regimen(
  amt = 100,
  times = c(0, 24, 36),
  type = "infusion"
)

mod <- new_ode_model("pk_3cmt_iv")
dat <- sim(
  ode = mod,
  parameters = p,
  omega = omega,
  n_ind = 20,
  regimen = r1
)
```

`sim_core` *Only core function of the simulation function, always just returns observations. Mostly useful for estimations / optimal design. Has no checks (for speed)!*

Description

Only core function of the simulation function, always just returns observations. Mostly useful for estimations / optimal design. Has no checks (for speed)!

Usage

```
sim_core(sim_object = NULL, ode, duplicate_t_obs = FALSE, t_init = 0)
```

Arguments

`sim_object`	list with design and simulation parameters
`ode`	ode
`duplicate_t_obs`	allow duplicate t_obs in output? E.g. for optimal design calculations when t_obs = c(0,1,2,2,3). Default is FALSE.
`t_init`	time of initization of the ODE system. Usually 0.

Value

Data frame with simulation results

`sim_ode` *Deprecated function, renamed to* `sim()`

Description

Deprecated function, renamed to `sim()`

Usage

```
sim_ode(...)
```

Arguments

`...`	parameters passed to `sim()` function

Value

Output from `sim()`

See Also

sim

`sim_ode_shiny` *Simulate ODE and create a Shiny app*

Description

This function has been deprecated and moved to a separate package at https://github.com/ronkeizer/PKPDsimshiny.

Usage

```
sim_ode_shiny(...)
```

Arguments

`...`	arguments passed to PKPDsimShiny::sim_ode_shiny()

Value

No return value

See Also

sim_ode

table_to_list *Convert a table to a list*

Description

Convert a table to a list

Usage

```
table_to_list(table)
```

Arguments

table	data.frame

Value

List containing original table contents

test_model *Test a model*

Description

Test a model

Usage

```
test_model(url, test_file, package, force = FALSE)
```

Arguments

url	URL or file path to JSON representation of model
test_file	Path to a .R file containing tests to run
package	Package name
force	Run tests even if model is not flagged for building? Defaults to FALSE

Value

Runs test file for a model but does not return a value

test_pointer *Test if model still in memory*

Description

Test if model still in memory

Usage

```
test_pointer(model)
```

Arguments

model	pointer to model

Value

No return value

ThreeCompIVbolus *IV bolus- 3 compartment*

Description

IV bolus- 3 compartment

Usage

```
ThreeCompIVbolus(d)
```

Arguments

d	data, Accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV,DV, CL, V1, Q12, V2, Q13, V3

Value

Returns a dataframe with populated columns for A1, A2, A3,and DV

ThreeCompIVinfusion *IV infusion- 3 compartment*

Description

IV infusion- 3 compartment

Usage

```
ThreeCompIVinfusion(d)
```

Arguments

d	data, Accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV,RATE, RATEALL, DV, CL, V1, Q12, V2, Q13, V3

Value

Returns a dataframe with populated columns for A1, A2, A3,and DV

ThreeCompIVinfusionMetab *3-compartment IV infusion with first-order metabolite formation*

Description

3-compartment IV infusion with first-order metabolite formation

Usage

```
ThreeCompIVinfusionMetab(d)
```

Arguments

d	data, accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV,RATE, RATEALL, DV, CL, V1, Q12, V2, Q13, V3, CLM,VM,km

Value

Returns a dataframe with populated columns for A1, A2, A3,and DV

ThreeCompOral *first-order absorption- 3 compartment*

Description

first-order absorption- 3 compartment

Usage

```
ThreeCompOral(d)
```

Arguments

d	data, accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV,DV, CL, V2, Q3, V3, Q4, V4, KA & F1

Value

Returns a dataframe with populated columns for A1, A2, A3, A4 and DV

ThreeCompOralMetab *first-order absorption- 3 compartment-Metabolite*

Description

first-order absorption- 3 compartment-Metabolite

Usage

```
ThreeCompOralMetab(d)
```

Arguments

d	data, accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV,DV, CL, V2, Q3, V3, Q4, V4, KA & F1

Value

Returns a dataframe with populated columns for A1, A2, A3, A4 and DV

translate_ode *Translate a model from/to various PKPD simulators*

Description

Currently only supports PKDPsim <–> RxODE

Usage

```
translate_ode(code, auto = TRUE, from = NULL, to = NULL, verbose = TRUE)
```

Arguments

code	character string with ODE code
auto	is auto-detect syntax (‘from‘)
from	from syntax
to	to syntax
verbose	verbose, ‘TRUE‘ or ‘FALSE‘

Value

Translated PKPDsim or RxODE model

triangle_to_full *Convert triangle omega matrix to full omega matrix*

Description

Convert triangle omega matrix to full omega matrix

Usage

```
triangle_to_full(vect)
```

Arguments

vect	vector specifying triangle omega matrix

Value

Omega matrix

TwoCompIVbolus *IV bolus- 2 compartment*

Description

IV bolus- 2 compartment

Usage

```
TwoCompIVbolus(d)
```

Arguments

d	data, accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV, DV, CL, V1, Q, V2

Value

Returns a dataframe with populated columns for A1, A2, and DV

TwoCompIVinfusion *IV infusion- 2 compartment*

Description

IV infusion- 2 compartment

Usage

```
TwoCompIVinfusion(d)
```

Arguments

d	data, accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV, RATE, RATEALL, DV, CL, V1, Q, V2

Value

Returns a dataframe with populated columns for A1, A2, and DV

TwoCompOral *First-order absorption- 2 compartment*

Description

First-order absorption- 2 compartment

Usage

```
TwoCompOral(d)
```

Arguments

d	data, accepts a NONMEM style data frame for 1 subject with columns for TIME, AMT,MDV,DV, CL, V2, Q, V3, KA & F1

Value

Returns a dataframe with populated columns for A1, A2, A3 and DV

vector_to_R_code *Transform a vector into a string that evaluates to the same vector*

Description

Collapses a vector into a comma-separated list with strings quoted (and special characters escaped). A general purpose helper function for writing new model code.

Usage

```
vector_to_R_code(vec)
```

Arguments

vec	a vector

Value

character string of length 1

Index