Package 'tci'

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Title Target Controlled Infusion (TCI)

Version 0.2.0

Description Implementation of target-controlled infusion algorithms for compartmental pharmacokinetic and pharmacokinetic-pharmacodynamic models. Jacobs (1990) <doi:10.1109/10.43622>; Marsh et al. (1991) <doi:10.1093/bja/67.1.41>; Shafer and Gregg (1993) <doi:10.100
199805000-00006>; Abuhelwa, Foster, and Upton (2015) <doi:10.1016/j.vascn.2015.03.004>; Eleveld et al. (2018) <doi:10.1016/j.bja.2018.01.018>.

Depends R (>= 3.6.0)

License GPL-2

Encoding UTF-8

LazyData true

URL https://github.com/jarretrt/tci

BugReports https://github.com/jarretrt/tci/issues

Imports ggplot2, stats, utils, truncnorm, mvtnorm, gridExtra, reshape, reshape2, xtable, Rcpp, knitr

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R topics documented:

`apply_tci` *Apply a TCI algorithm to a 'pkmod' object*

Description

Apply a TCI algorithm to a set of targets and a 'pkmod' object to calculate infusion rates.

Usage

```
apply_tci(
  pkmod,
  target_vals,
  target_tms,
  type = c("plasma", "effect"),
  dtm = NULL,
  custom_alg = NULL,
  inittm = 0,
  ignore_pd = FALSE,
  ...
)
```

Arguments

`pkmod`	'pkmod' object created by 'pkmod()'.
`target_vals`	A vector of numeric values indicating PK or PD targets for TCI algorithm.
`target_tms`	A vector of numeric values indicating times at which the TCI algorithm should begin targeting each value.
`type`	Type of TCI algorithm to be used. Options are plasma- or effect-site targeting.
`dtm`	TCI update frequency. Defaults to 1/6, corresponding to 10-second intervals if model parameters are in terms of minutes.
`custom_alg`	Custom TCI algorithm to be used instead of default plasma- or effect-site targeting algorithms. The algorithm should be a function that takes minimum arguments 'Ct', 'pkmod', and 'dtm' and returns a single infusion rate. See 'tci_plasma' or 'tci_effect' for examples and vignette on custom models/algorithms for more details.
`inittm`	Initial time to start TCI algorithm. Cannot be greater than the minimum value of 'target_tms'.

ignore_pd	Logical. Should the PD component of the pkmod object (if present) be ignored. By default, predict.tciinf will assume that 'value' refers to PD targets if a PD model is specified.
...	Arguments passed to TCI algorithm

Examples

```
# 3-compartment model with effect-site
my_mod <- pkmod(pars_pk = c(v1 = 8.995, v2 = 17.297, v3 = 120.963, cl = 1.382,
q2 = 0.919, q3 = 0.609, ke0 = 1.289))
# plasma targeting
apply_tci(my_mod, target_vals = c(2,3,4,4), target_tms = c(0,2,3,10), "plasma")
# effect-site targeting
apply_tci(my_mod, target_vals = c(2,3,4,4), target_tms = c(0,2,3,10), "effect")
# incorporate  PD model
my_mod_pd <- update(my_mod, pars_pd = c(c50 = 2.8, gamma = 1.47, e0 = 93, emx = 93),
pdfn = emax, pdinv = emax_inv)
apply_tci(my_mod_pd, target_vals = c(70,60,50,50), target_tms = c(0,2,3,10), "effect")
```

---

assign_pars *Set default PK parameter values Set default PK parameter values for a pkmod object.*

Description

Set default PK parameter values Set default PK parameter values for a pkmod object.

Usage

```
assign_pars(pkmod, pars)
```

Arguments

pkmod	pkmod object
pars	PK parameters to assign as default values of pkmod

Value

pkmod object

bayes_update *Update PK-PD model parameters using observed data values*

Description

Function will update parameters of ‘pkmod‘ object based on available data using a Laplace approximation to the posterior. Parameters and "Omega" values from ‘pkmod‘ are used as prior point estimates and variance terms, respectively. Parameters fixed within the Omega matrix are assumed to be fixed and are not updated.

Usage

```
bayes_update(lpars, pkmod, inf, tms, obs, update_init = FALSE, ...)
```

Arguments

lpars	Logged parameter values. Can be a subset of the full set of PK or PK-PD parameter values.
pkmod	‘pkmod‘ object. Mean values are a subset of log(pars_pk), log(pars_pd), log(sigma_add), log(sigma_mult). PK-PD parameter values not specified in ‘lpars‘ will be inferred from ‘pkmod‘.
inf	Infusion schedule
tms	Times associated with observations
obs	Observed values (concentrations or PD response values)
update_init	Logical. Should initial values be updated in addition to parameter values?
...	Arguments passed to update.pkmod

Value

‘pkmod‘ object with PK/PK-PD/sigma parameters updated based on minimizing negative logged posterior.

Examples

```
# evaluate negative log posterior at a new set of parameters
lpars = log(c(cl=11,q2=3,q3=25,v=20,v2=40,v3=80,ke0=1.15,sigma_add=0.3))
prior_vcov <- matrix(diag(c(0.265,0.346,0.209,0.610,0.565,0.597,0.702,0.463)),
8,8, dimnames = list(NULL,names(lpars)))
my_mod <- pkmod(pars_pk = c(cl = 10, q2 = 2, q3 =20, v = 15, v2 = 30, v3 = 50, ke0 = 1.2),
sigma_add = 0.2, log_response = TRUE, Omega = prior_vcov)
inf <- inf_manual(inf_tms = 0, inf_rate = 80, duration = 2)
tms <- c(1,2,4,8,12)
obs <- simulate(my_mod, inf = inf, tms = tms)
bayes_update(lpars, my_mod, inf, tms, obs)

# evaluate log-prior for subset of parameters (remove volume parameters)
```

```
lpars_sub = log(c(cl=11,q2=3,q3=25,ke0=1.15,sigma_add=0.15))
my_mod <- update(my_mod, Omega = matrix(diag(c(0.265,0.346,0.209,0.702,0.463)),5,5,
 dimnames = list(NULL,names(lpars_sub))))
bayes_update(lpars_sub, my_mod, inf, tms, obs)

# add a pd response and replace multiplicative error with additive error
my_mod_pd <- update(my_mod, pars_pd = c(c50 = 2.8, gamma = 1.47, e0 = 93, emx = 93),
pdfn = emax, pdinv = emax_inv, ecmpt = 4, sigma_mult = 0, sigma_add = 4)
# simulate observations
obs_pd <- simulate(my_mod_pd, inf = inf, tms = seq(0,12,0.5))
# evaluate likelihood at new parameters
lpars_pd_eval = log(c(cl=11,q3=25,v=15,ke0=1.15,sigma_add=4,c50=5,gamma=1))
prior_vcov_pd <- matrix(diag(c(0.265,0.209,0.610,0.702,0.230,0.242,0.1)),7,7,
dimnames = list(NULL,names(lpars_pd_eval)))
my_mod_pd <- update(my_mod_pd, Omega = prior_vcov_pd)
bayes_update(lpars_pd_eval, my_mod_pd, inf, tms, obs_pd)
```

`clc` *Simulate closed-loop control*

Description

Simulate closed-loop control using Bayesian updates. Infusion rates are calculated using ‘pkmod_prior‘ to reach ‘target_vals‘ at ‘target_tms‘. Data values are simulated using ‘pkmod_true‘ at ‘obs_tms‘. ‘pkmod_prior‘ and ‘pkmod_true‘ do not need to have the same structure. Model parameters are updated at each update time using all available simulated observations. Processing delays can be added through the ‘delay‘ argument, such that observations aren’t made available to the update mechanism until ‘update_tms >= obs_tms + delay‘.

Usage

```
clc(
  pkmod_prior,
  pkmod_true,
  target_vals,
  target_tms,
  obs_tms,
  update_tms,
  type = c("effect", "plasma"),
  custom_alg = NULL,
  resp_bounds = NULL,
  delay = 0,
  seed = NULL
)
```

Arguments

`pkmod_prior`	‘pkmod‘ object describing a PK/PK-PD model that is used to calculate TCI infusion rates and is updated as data are simulated and incorporated. Must have an associated Omega matrix.

pkmod_true	‘pkmod‘ object describing the patient’s "true" response. This model will be used to simulate observations.
target_vals	A vector of numeric values indicating PK or PD targets for TCI algorithm.
target_tms	A vector of numeric values indicating times at which the TCI algorithm should begin targeting each value.
obs_tms	Times at which data values should be simulated from ‘pkmod_true‘.
update_tms	Times at which ‘pkmod_prior‘ should be updated using all available simulated observations.
type	Type of TCI algorithm to be used. Options are "plasma" and "effect". Defaults to "effect". Will be overwritten if ‘custom_alg‘ is non-null.
custom_alg	Custom TCI algorithm to overwrite default plasma- or effect-site targeting.
resp_bounds	Optional vector of two values indicating minimum and maximum values possible for the response.
delay	Optional numeric value indicating a temporal delay between when observations are simulated and when they should be made available for updating ‘pkmod_prior‘. For example, a delay should be set to account for a processing time delay in Bispectral Index measurements or the time required to measure drug concentrations from collected samples.
seed	An integer used to initialize the random number generator.

Examples

```
prior_vcov <- matrix(diag(c(0.265,0.346,0.209,0.610,0.565,0.597,0.702,0.463)),
8,8, dimnames = list(NULL,c('cl','q2','q3','v','v2','v3','ke0','sigma_add')))
pkmod_prior <- pkmod(pars_pk = c(cl = 10, q2 = 2, q3 =20, v = 15, v2 = 30, v3 = 50, ke0 = 1.2),
sigma_add = 0.2, log_response = TRUE, Omega = prior_vcov)
pkmod_true  <- pkmod(pars_pk = c(cl = 16, q2 = 4, q3 =10, v = 20, v2 = 20, v3 = 80, ke0 = 0.8),
sigma_add = 0.1, log_response = TRUE)
target_vals <- c(2,3,4,3,3)
target_tms <- c(0,5,10,36,60)
obs_tms <- c(1,2,4,8,12,16,24,36,48)
update_tms <- c(5,15,25,40,50)
sim <- clc(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms, update_tms, seed = 200)
len <- 500
tms <- seq(0,60,length.out = len)
# true, prior, posterior plasma concentrations
df <- data.frame(time = rep(tms,3),
                 value = c(predict(pkmod_true, sim$inf,tms)[,1],
                 predict(pkmod_prior, sim$inf,tms)[,1],
                 predict(sim$pkmod_post, sim$inf, tms)[,1]),
                 type = c(rep("true",len),rep("prior",len),rep("posterior",len)))
library(ggplot2)
ggplot(df, aes(x = time, y = value, color = type)) +
  geom_line() +
  geom_point(data = sim$obs, aes(x = time, y = obs), inherit.aes = FALSE) +
  geom_step(data = data.frame(time = target_tms, value = target_vals),
  aes(x = time, y = value), inherit.aes = FALSE)
```

```
# PK-PD example with observation delay (30 sec)
prior_vcov <- matrix(diag(c(0.265,0.346,0.209,0.702,0.242,0.230)),6,6,
dimnames = list(NULL,c('cl','q2','q3','ke0','c50','sigma_add')))
pkpdmod_prior <- update(pkmod_prior, pars_pd = c(c50 = 2.8, gamma = 1.47, e0 = 93, emx = 93),
pdfn = emax, pdinv = emax_inv, sigma_add = 4, log_response = FALSE, Omega = prior_vcov)
pkpdmod_true <- update(pkmod_true, pars_pd = c(c50 = 3.4, gamma = 1.47, e0 = 93, emx = 93),
pdfn = emax, pdinv = emax_inv, sigma_add = 3, log_response = FALSE)
target_vals <- c(75,60,50,50)
target_tms <- c(0,3,6,10)
obs_tms <- seq(1/6,10,1/6)
update_tms <- seq(1,10,0.5)
## Not run:
sim_pkpd <- clc(pkpdmod_prior, pkpdmod_true, target_vals, target_tms, obs_tms,
update_tms, seed = 201, delay = 0.5)
# plot results
tms <- seq(0,10,length.out = len)
df <- data.frame(time = rep(tms,3),
                 value = c(predict(pkpdmod_true, sim_pkpd$inf,tms)[,"pdresp"],
                 predict(pkpdmod_prior, sim_pkpd$inf,tms)[,"pdresp"],
                 predict(sim_pkpd$pkmod_post, sim_pkpd$inf, tms)[,"pdresp"]),
                 type = c(rep("true",len),rep("prior",len),rep("posterior",len)))
library(ggplot2)
ggplot(df, aes(x = time, y = value, color = type)) +
  geom_line() +
  geom_point(data = sim_pkpd$obs, aes(x = time, y = obs), inherit.aes = FALSE) +
  labs(x = "Hours", y = "Bispectral Index") + theme_bw() +
  geom_vline(xintercept = update_tms, linetype = "dotted", alpha = 0.6) +
  geom_step(data = data.frame(time = target_tms, value = target_vals),
  aes(x = time, y = value), inherit.aes = FALSE)

## End(Not run)
```

`eleveld_pd` *Eleveld et al. pharmacodynamic data*

Description

Empirical Bayes (EB) estimates of PD parameters made by the Eleveld et al (2018) PK-PD model. EB estimates were calculated using the PK-PD datasets and NONMEM files provided by Eleveled et al. (2018). The original datasets were obtained through the Open TCI Initiative website (opentci.org) and based on contributions from a number of researchers who made their datasets publically available.

Usage

```
data(eleveld_pd)
```

Format

A data frame with 122 rows and 15 variables:

ID Patient ID

E50 EB estimate of effect-site concentration required to achieve 50 percent response

KE0 EB estimate of elimination rate from effect-site compartment

EMAX EB estimate of baseline bispectral index (BIS) with no drug administered

GAM EB estimate of Hill parameter when the effect-site concentration is less than E50

GAM1 EB estimate of Hill parameter when the effect-site concentration is greater than than E50

RESD EB estimate of residual error term

ALAG1 Estimated time lag in BIS measurements due to patient age (fixed-effects only)

AGE Patient's age (years)

WGT Patient's weight (kg)

HGT Patient's height (cm)

M1F2 Patient's sex: male = 1, female = 2

A1V2 Sampling site: arterial sampling = 1, venous sampling = 2

PMA Patient's post-menstrual age. Assumed to be age + 40 weeks if not provided

TECH Presence of concomitant anaesthetic techniques (Local anesthetic = 1, Opioids = 2)

References

Eleveld et al. (2018) British Journal of Anesthesia Vol. 120, 5:942-959 (BJA)

`eleveld_pk` *Eleveld et al. pharmacokinetic data*

Description

Empirical Bayes (EB) estimates of PK parameters for the Eleveld et al. (2018) PK-PD model. EB estimates were calculated using the PK-PD datasets and NONMEM files provided by Eleveled et al. (2018). The original datasets were obtained through the Open TCI Initiative website (opentci.org) and based on contributions from a number of researchers who made their datasets publically available.

Usage

```
data(eleveld_pk)
```

Format

A data frame with 1033 rows and 16 variables:

ID Patient ID

V1 EB estimate of first compartment volume

V2 EB estimate of second compartment volume

V3 EB estimate of third compartment volume

CL EB estimate of clearance for the first compartment

Q2 EB estimate of inter-compartmental clearance for second compartment

Q3 EB estimate of inter-compartmental clearance for third compartment

AGE Patient's age (years)

WGT Patient's weight (kg)

HGT Patient's height (cm)

M1F2 Patient's sex: male = 1, female = 2

PMA Patient's post-menstrual age. Assumed to be age + 40 weeks if not provided

TECH Presence of concomitant anaesthetic techniques (Local anesthetic = 1, Opioids = 2)

BMI Patient's BMI

FFM Patient's fat-free mass (FFM)

A1V2 Sampling site: arterial sampling = 1, venous sampling = 2

References

Eleveld et al. (2018) British Journal of Anesthesia Vol. 120, 5:942-959 (BJA)

`elvdlpars` *Get logged parameters updated in Eleveld model*

Description

Extract the logged parameter values to be updated within the Eleveld model from a data frame of patient PK-PD values.

Usage

```
elvdlpars(x, pd = TRUE)
```

Arguments

`x`	Vector or data frame with Eleveld PK-PD model parameters
`pd`	Logical. Should PD parameters be returned in addition to PK parameters.

Value

List of parameters used by Eleveld PK-PD model.

emax *Emax function*

Description

Emax function. c50 is the concentration eliciting a 50 identifying the slope of the Emax curve at c50, E0 is the response value with no drug present, Emx is the maximum effect size.

Usage

```
emax(ce, pars)
```

Arguments

ce	Vector of effect-site concentrations.
pars	Named vector of parameter values with names (c50,gamma,e0,emx).

Value

Numeric vector of same length as ce.

Examples

```
pars_emax <- c(c50 = 1.5, gamma = 1.47, e0 = 100, emx = 100)
ce_seq <- seq(0,4,0.1)
plot(ce_seq, emax(ce_seq, pars_emax), type = "l",
xlab = "Effect-site concentrtion (ug/mL)", ylab = "BIS")
```

emax_eleveld *Emax function for Eleveld (2018) model.*

Description

The parameter gamma takes one of two values depending on whether ce <= c50.

Usage

```
emax_eleveld(ce, pars)
```

Arguments

ce	Vector of effect-site concentrations.
pars	Vector of parameter values in order (c50,gamma,gamma2,e0,emx).

Value

Numeric vector of same length as ce.

Examples

```
pars_emax_eleveld <- c(c50 = 1.5, e0 = 100, gamma = 1.47, gamma2 = 1.89)
ce_seq <- seq(0,4,0.1)
plot(ce_seq, emax_eleveld(ce_seq, pars_emax_eleveld), type = "l",
xlab = "Effect-site concentrtion (ug/mL)", ylab = "BIS")
```

`emax_inv` *Inverse Emax function*

Description

Inverse Emax function to return effect-site concentrations required to reach target effect.

Usage

```
emax_inv(pdresp, pars)
```

Arguments

`pdresp`	PD response values
`pars`	Named vector of parameter values with names (c50,gamma,E0,Emx).

Value

Numeric vector of same length as pdresp.

Examples

```
pars_emax <- c(c50 = 1.5, gamma = 4, e0 = 100, emx = 100)
ce_seq <- seq(0,4,0.1)
all.equal(emax_inv(emax(ce_seq, pars_emax), pars_emax), ce_seq)
```

`emax_inv_eleveld` *Inverse Emax function*

Description

Inverse of Emax function used by Eleveld population PK model.

Usage

```
emax_inv_eleveld(pdresp, pars)
```

Arguments

`pdresp`	PD response values
`pars`	Named vector of parameter values with names (c50,gamma,E0,Emx).

Value

Numeric vector of same length as pdresp.

Examples

```
pars_emax_eleveld <- c(c50 = 1.5, e0 = 100, gamma = 1.47, gamma2 = 1.89)
ce_seq <- seq(0,4,0.1)
all.equal(emax_inv_eleveld(emax_eleveld(ce_seq, pars_emax_eleveld), pars_emax_eleveld), ce_seq)
```

---

emax_inv_remi *Inverse Emax function implemented by Eleveld remifentanil model*

Description

Inverse Emax function to return effect-site concentrations required to reach target effect.

Usage

```
emax_inv_remi(pdresp, pars)
```

Arguments

pdresp	PD response values
pars	Named vector of parameter values with names (c50,gamma,E0,Emx).

Value

Numeric vector of same length as pdresp.

Examples

```
pars_emax <- c(e0 = 19, emx = 5.6, c50 = 12.7, gamma = 2.87)
emax_inv_remi(emax_remi(10, pars_emax), pars_emax)
```

---

emax_remi *Emax function implemented by Eleveld remifentanil model*

Description

Emax function. c50 is the concentration eliciting a 50 identifying the slope of the Emax curve at c50, E0 is the response value with no drug present, Emx is the maximum effect size.

Usage

```
emax_remi(ce, pars)
```

Arguments

ce	Vector of effect-site concentrations.
pars	Named vector of parameter values with names (c50,gamma,e0,emx).

Value

Numeric vector of same length as ce.

Examples

```
pars_emax <- c(e0 = 19, emx = 5.6, c50 = 12.7, gamma = 2.87)
ce_seq <- seq(0,60,0.1)
plot(ce_seq, emax_remi(ce_seq, pars_emax), type = "l",
xlab = "Effect-site concentrtion (ug/mL)", ylab = "Spectral Edge Frequency (HZ)")
```

---

format_pars *Format parameters for use in Rcpp functions Order parameters for 1-4 compartment models to be used in Rcpp functions in predict_pkmod method.*

Description

Format parameters for use in Rcpp functions

Order parameters for 1-4 compartment models to be used in Rcpp functions in predict_pkmod method.

Usage

```
format_pars(pars, ncmpt = 3)
```

Arguments

pars	Vector of named parameters. Names can be capitalized or lowercase and can include variations of "V1" as "V" or clearance terms rather than elimination rate constants.
ncmpt	Number of compartments in the model. This should be a value between 1 and 4. If ncmpt = 4, it assumes that the fourth compartment is an effect-site without a corresponding volume parameter.

Value

Numeric vector of transformed parameter values.

Examples

```
format_pars(c(V1 = 8.9, CL = 1.4, q2 = 0.9, v2 = 18), ncmpt = 2)
format_pars(c(V1 = 8.9, CL = 1.4, q2 = 0.9, v2 = 18, cl2 = 3), ncmpt = 2)
```

infer_pkfn *Identify pkfn from parameter names*

Description

Identify structural PK model function (i.e., 'pkfn') from parameter names. Models available are 1-, 2-, and 3-compartment mammillary models, or 3-compartment with an effect site, corresponding to functions 'pkmod1cpt', 'pkmod2cpt', 'pkmod3cpt', and 'pkmod3cptm', respectively.

Usage

```
infer_pkfn(parnms)
```

Arguments

parnms	Vector of parameter names.

Value

Returns one of the following functions: 'pkmod1cpt', 'pkmod2cpt', 'pkmod3cpt', or 'pkmod3cptm' based on the parameter names entered.

Examples

```
# 1-compartment
infer_pkfn(c("CL","V"))
infer_pkfn(c("Cl","v1"))
# 2-compartment
infer_pkfn(c("CL","v","v2","q"))
# 3-compartment
infer_pkfn(c("CL","v","v2","q","Q2","V3"))
# 3-compartment with effect-site
infer_pkfn(c("CL","v","v2","q","Q2","V3","ke0"))
```

inf_manual *infusion schedule*

Description

Returns a data frame describing a set of infusions to be administered. Output can be used as argument "inf" in predict_pkmod.

Usage

```
inf_manual(inf_tms, inf_rate, duration = NULL)
```

Arguments

inf_tms	Vector of time to begin infusions. If duration is NULL, times expected to include both infusion start and infusion end times.
inf_rate	Vector of infusion rates. Must lave length equal to either length(inf_tms) or 1. If length(inf_rate)=1, the same infusion rate will be administered at each time. Either inf_rate or target must be specified, but not both.
duration	Optional duration of infusions.

Value

Matrix of infusion rates, start and end times.

Examples

```
# specify start and end times, as well as infusion rates (including 0).
inf_manual(inf_tms = c(0,0.5,4,4.5,10), inf_rate = c(100,0,80,0,0))
# specify start times, single infusion rate and single duration
inf_manual(inf_tms = c(0,4), inf_rate = 100, duration = 0.5)
# multiple infusion rates, single duration
inf_manual(inf_tms = c(0,4), inf_rate = c(100,80), duration = 0.5)
# multiple sequential infusion rates
inf_manual(inf_tms = seq(0,1,1/6), inf_rate = 100, duration = 1/6)
# single infusion rate, multiple durations
inf_manual(inf_tms = c(0,4), inf_rate = 100, duration = c(0.5,1))
# multiple infusion rates, multiple durations
inf_manual(inf_tms = c(0,4), inf_rate = c(100,80), duration = c(0.5,1))
```

---

inf_tci *Target-controlled infusion*

Description

Apply a TCI algorithm to a set of targets and a ‘pkmod‘ or ‘poppkmod‘ object to calculate infusion rates.

Usage

```
inf_tci(
  pkmod,
  target_vals,
  target_tms,
  type = c("plasma", "effect"),
  dtm = NULL,
  custom_alg = NULL,
  inittm = 0,
  ignore_pd = FALSE,
  ...
)
```

Arguments

pkmod	‘pkmod‘ object created by ‘pkmod()‘ or a ‘poppkmod‘ object created by ‘poppkmod()‘.
target_vals	A vector of numeric values indicating PK or PD targets for TCI algorithm.
target_tms	A vector of numeric values indicating times at which the TCI algorithm should begin targeting each value.
type	Type of TCI algorithm to be used. Options are plasma- or effect-site targeting.
dtm	TCI update frequency. Defaults to 1/6, corresponding to 10-second intervals if model parameters are in terms of minutes.
custom_alg	Custom TCI algorithm to be used instead of default plasma- or effect-site targeting algorithms. The algorithm should be a function that takes minimum arguments ‘Ct‘, ‘pkmod‘, and ‘dtm‘ and returns a single infusion rate. See ‘tci_plasma‘ or ‘tci_effect‘ for examples and vignette on custom models/algorithms for more details.
inittm	Initial time to start TCI algorithm. Cannot be greater than the minimum value of ‘target_tms‘.
ignore_pd	Logical. Should the PD component of the pkmod object (if present) be ignored. By default, predict.tciinf will assume that ’value’ refers to PD targets if a PD model is specified.
...	Arguments passed to TCI algorithm

Examples

```
# 3-compartment model with effect-site
my_mod <- pkmod(pars_pk = c(v1 = 8.995, v2 = 17.297, v3 = 120.963, cl = 1.382,
q2 = 0.919, q3 = 0.609, ke0 = 1.289))
# plasma targeting
inf_tci(my_mod, target_vals = c(2,3,4,4), target_tms = c(0,2,3,10), "plasma")
# effect-site targeting
inf_tci(my_mod, target_vals = c(2,3,4,4), target_tms = c(0,2,3,10), "effect")
# poppkmod object
data <- data.frame(ID = 1:5, AGE = seq(20,60,by=10), TBW = seq(60,80,by=5),
HGT = seq(150,190,by=10), MALE = c(TRUE,TRUE,FALSE,FALSE,FALSE))
elvd_mod <- poppkmod(data, drug = "ppf", model = "eleveld")
inf_tci(elvd_mod, target_vals = c(2,3,4,4), target_tms = c(0,2,3,10), "effect")
```

---

init_pkmod *Create an object with class "pkmod"*

Description

Create an object with class "pkmod"

Usage

```
init_pkmod(
  pars_pk = NULL,
  init = NULL,
  pkfn = NULL,
  pars_pd = NULL,
  pdfn = NULL,
  pdinv = NULL,
  pcmpt = NULL,
  ecmpt = NULL,
  sigma_add = NULL,
  sigma_mult = NULL,
  log_response = NULL,
  Omega = NULL
)
```

Arguments

pars_pk	Vector or matrix of named PK parameters. If not specified, the pkmod function will be inferred from the parameter names. Print 'list_parnms()' for acceptable parameter names.
init	Vector of initial concentrations. Will default to values of zero in all compartments if not specified.
pkfn	PK model function. Functions provided in 'tci' include 'pkmod1cpt', 'pkmod2cpt', 'pkmod3cpt', and 'pkmod3cptm'. User-defined functions should be specified here.
pars_pd	PD model parameters if a PD model is specified
pdfn	PD model function
pdinv	Inverse PD model function for use in TCI algorithms
pcmpt	Index of plasma compartment. Defaults to first compartment if not specified.
ecmpt	Index of effect-site compartment if a PD model is specified. Will default to last compartment if unspecified.
sigma_add	Standard deviation of additive residual error
sigma_mult	Standard deviation of multiplicative residual error
log_response	Logical value indicating if the response should be logged prior to adding error.
Omega	Optional matrix of random effect parameters. Column names should correspond to names of pars_pk, pars_pd, and sigma_add or sigma_mult.

Value

A list with class pkmod for which print, plot, predict, and simulate methods exist.

Examples

```
# create a pkmod object for a one compartment model with plasma targeting
init_pkmod()
```

`init_poppkmod` *Initialize a 'poppkmod' object.*

Description

Generate a 'poppkmod' object from an existing population PK model for propofol or remifentanil using patient covariates. Available models for propofol are the Marsh, Schnider, and Eleveld models. Available models for remifentanil are the Minto, Kim, and Eleveld models. Input is a data frame with rows corresponding to individuals and columns recording patient covariates.

Usage

```
init_poppkmod(data = NULL, drug = NULL, model = NULL, sample = NULL, PD = NULL)
```

Arguments

`data`	Data frame of patient covariates. ID values, if used, should be in a column labeled "id" or "ID"
`drug`	"ppf" for propofol or "remi" for remifentanil. Defaults to "ppf".
`model`	Model name. Options are "marsh", "schnider", or "eleveld" if drug = "ppf", or "minto", "kim", or "eleveld" if drug = "remi".
`sample`	Logical. Should parameter values be sampled from interindividual distribution (TRUE) or evaluated at point estimates for covariates (FALSE)? Defaults to FALSE.
`PD`	Should the PD component be evaluated for PK-PD models. Defaults to TRUE.

Value

'poppkmod' object

Examples

```
data <- data.frame(ID = 1:5, AGE = seq(20,60,by=10), TBW = seq(60,80,by=5),
HGT = seq(150,190,by=10), MALE = c(TRUE,TRUE,FALSE,FALSE,FALSE))
init_poppkmod(data, drug = "ppf", model = "eleveld")
init_poppkmod(data, drug = "remi", model = "kim")
```

list_parnms *Identify pkfn from parameter names*

Description

Identify structural PK model function (i.e., 'pkfn') from parameter names. Models available are 1-, 2-, and 3-compartment mammillary models, or 3-compartment with an effect site, corresponding to functions 'pkmod1cpt', 'pkmod2cpt', 'pkmod3cpt', and 'pkmod3cptm', respectively.

Usage

```
list_parnms()
```

Value

Returns one of the following functions: 'pkmod1cpt', 'pkmod2cpt', 'pkmod3cpt', or 'pkmod3cptm' based on the parameter names entered.

Examples

```
list_parnms()
```

list_pkmods *Print population PK models available in 'tci'*

Description

Print population PK models available in 'tci' for propofol (Marsh, Schnider, Eleveld) and remifentanil (Minto, Kim, Eleveld).

Usage

```
list_pkmods()
```

Value

Prints function names, model types, and required covariates for each model.

Examples

```
list_pkmods()
```

log_likelihood *Evaluate the log likelihood of a vector of parameter values*

Description

Evaluate the log liklihood of parameters given observed data. Can be applied to PK or PK-PD models.

Usage

```
log_likelihood(lpars, pkmod, inf, tms, obs)
```

Arguments

lpars	Named vector of logged parameter values to be evaluated. This should include any PK or PD parameters, as well as residual error standard deviations (sigma_add or sigma_mult) that are to be evaluated.
pkmod	'pkmod' object. Mean values are a subset of log(pars_pk), log(pars_pd), log(sigma_add), log(sigma_mult). PK-PD parameter values not specified in 'lpars' will be inferred from 'pkmod'.
inf	Infusion schedule
tms	Times associated with observations
obs	Observed values (concentrations or PD response values)

Value

Numeric value of length 1

Examples

```
my_mod <- pkmod(pars_pk = c(cl = 10, q2 = 2, q3 =20, v = 15, v2 = 30, v3 = 50,
 ke0 = 1.2), sigma_mult = 0.2)
inf <- inf_manual(inf_tms = 0, inf_rate = 80, duration = 2)
tms <- c(1,2,4,8,12)
obs <- simulate(my_mod, inf = inf, tms = tms)
# evaluate log-likelihood at a new set of parameters
lpars = log(c(cl=11,q2=3,q3=25,v=15,v2=30,v3=50,ke0=1.15,sigma_mult=0.3))
log_likelihood(lpars, my_mod, inf, tms, obs)

# estimate for a subset of parameters (exclude q2, v2, v3)
lpars_sub = log(c(cl=11,q3=25,v=15,ke0=1.15,sigma_mult=0.3))
log_likelihood(lpars_sub, my_mod, inf, tms, obs)

# add a pd response and replace multiplicative error with additive error
my_mod_pd <- update(my_mod, pars_pd = c(c50 = 2.8, gamma = 1.47, e0 = 93,
emx = 93), pdfn = emax, pdinv = emax_inv, ecmpt = 4, sigma_mult = 0, sigma_add = 4)
# simulate observations
obs_pd <- simulate(my_mod_pd, inf = inf, tms = seq(0,12,0.5))
```

```
# evaluate likelihood at new parameters
lpars_pd <- log(c(cl=11,q3=25,v=15,ke0=1.15,sigma_add=4,c50=5,gamma=1))
log_likelihood(lpars_pd, my_mod_pd, inf, tms = seq(0,12,0.5), obs_pd)
```

`log_posterior_neg` *Evaluate the negative log posterior value of a parameter vector*

Description

Evaluate the negative log posterior value of a parameter vector given a set of observations and prior distribution for log-normally distributed PK or PK-PD parameters.

Usage

```
log_posterior_neg(lpars, pkmod, inf, tms, obs)
```

Arguments

`lpars`	Logged parameter values. Can be a subset of the full set of PK or PK-PD parameter values.
`pkmod`	'pkmod' object. Mean values are a subset of log(pars_pk), log(pars_pd), log(sigma_add), log(sigma_mult). PK-PD parameter values not specified in 'lpars' will be inferred from 'pkmod'.
`inf`	Infusion schedule
`tms`	Times associated with observations
`obs`	Observed values (concentrations or PD response values)

Value

Numeric value of length 1

Examples

```
# evaluate negative log posterior at a new set of parameters
lpars = log(c(cl=11,q2=3,q3=25,v=20,v2=40,v3=80,ke0=1.15,sigma_add=0.3))
prior_vcov <- matrix(diag(c(0.265,0.346,0.209,0.610,0.565,0.597,0.702,0.463)),
8,8, dimnames = list(NULL,names(lpars)))
my_mod <- pkmod(pars_pk = c(cl = 10, q2 = 2, q3 =20, v = 15, v2 = 30, v3 = 50,
ke0 = 1.2), sigma_add = 0.2, log_response = TRUE, Omega = prior_vcov)
inf <- inf_manual(inf_tms = 0, inf_rate = 80, duration = 2)
tms <- c(1,2,4,8,12)
obs <- simulate(my_mod, inf = inf, tms = tms)
log_posterior_neg(lpars, my_mod, inf, tms, obs)

# evaluate log-prior for subset of parameters (remove volume parameters)
lpars_sub = log(c(cl=11,q2=3,q3=25,ke0=1.15,sigma_add=0.15))
my_mod <- update(my_mod, Omega = matrix(diag(c(0.265,0.346,0.209,0.702,0.463)),
5,5, dimnames = list(NULL,names(lpars_sub))))
```

```
log_posterior_neg(lpars_sub, my_mod, inf, tms, obs)

# add a pd response and replace multiplicative error with additive error
# evaluate likelihood at new parameters
lpars_pd_eval = log(c(cl=11,q3=25,v=15,ke0=1.15,sigma_add=4,c50=5,gamma=1))
prior_vcov_pd <- matrix(diag(c(0.265,0.209,0.610,0.702,0.230,0.242,0.1)),7,7,
dimnames = list(NULL,names(lpars_pd_eval)))
my_mod_pd <- update(my_mod, pars_pd = c(c50 = 2.8, gamma = 1.47, e0 = 93, emx = 93),
pdfn = emax, pdinv = emax_inv, ecmpt = 4, sigma_mult = 0, sigma_add = 4,
Omega = prior_vcov_pd)
# simulate observations
obs_pd <- simulate(my_mod_pd, inf = inf, tms = seq(0,12,0.5))
log_posterior_neg(lpars_pd_eval, my_mod_pd, inf, tms, obs_pd)
```

`log_prior` *Calculate logged-prior probability for a set of parameters*

Description

Calculate logged-prior probability for a set of parameters, assuming that parameter values are log-normally distributed. Mean values are set as the logged parameter values in the 'pkmod' object. Variances are given by the diagonal elements of 'prior_vcov'.

Usage

```
log_prior(lpars, pkmod)
```

Arguments

`lpars`	Logged parameter values. Can be a subset of the full set of PK or PK-PD parameter values.
`pkmod`	'pkmod' object. Mean values are a subset of log(pars_pk), log(pars_pd), log(sigma_add), log(sigma_mult). PK-PD parameter values not specified in 'lpars' will be inferred from 'pkmod'.

Value

Numeric value of length 1

Examples

```
# evaluate log-prior for pk parameters + residual
lpars = log(c(cl=11,q2=3,q3=25,v=15,v2=30,v3=50,ke0=1.15,sigma_add=0.15))
prior_vcov <- matrix(diag(c(0.265,0.346,0.209,0.610,0.565,0.597,0.702,0.463)), 8,8,
dimnames = list(NULL,names(lpars)))
my_mod <- pkmod(pars_pk = c(cl = 10, q2 = 2, q3 =20, v = 15, v2 = 30, v3 = 50, ke0 = 1.2),
sigma_add = 0.2, log_response = TRUE, Omega = prior_vcov)
log_prior(lpars, my_mod)
```

```
# evaluate log-prior for subset of parameters (remove volume parameters)
lpars_sub = log(c(cl=11,q2=3,q3=25,ke0=1.15,sigma_add=0.15))
prior_vcov_sub <- matrix(diag(c(0.265,0.346,0.209,0.702,0.463)), 5,5,
dimnames = list(NULL,names(lpars_sub)))
my_mod <- update(my_mod, Omega = prior_vcov_sub)
log_prior(lpars_sub, my_mod)
```

`olc` *Simulate open-loop control*

Description

Simulate open-loop control with target-controlled infusion for a ‘pkmod‘ object. Infusion rates are calculated using ‘pkmod_prior‘ to reach ‘target_vals‘ at ‘target_tms‘. Data values are simulated using ‘pkmod_true‘ at ‘obs_tms‘. ‘pkmod_prior‘ and ‘pkmod_true‘ do not need to have the same structure.

Usage

```
olc(
  pkmod_prior,
  pkmod_true,
  target_vals,
  target_tms,
  obs_tms,
  type = c("effect", "plasma"),
  custom_alg = NULL,
  resp_bounds = NULL,
  seed = NULL
)
```

Arguments

`pkmod_prior`	‘pkmod‘ object describing a PK/PK-PD model that is used to calculate TCI infusion rates and is updated as data are simulated and incorporated. Must have an associated Omega matrix.
`pkmod_true`	‘pkmod‘ object describing the patient’s "true" response. This model will be used to simulate observations.
`target_vals`	A vector of numeric values indicating PK or PD targets for TCI algorithm.
`target_tms`	A vector of numeric values indicating times at which the TCI algorithm should begin targeting each value.
`obs_tms`	Times at which data values should be simulated from ‘pkmod_true‘.
`type`	Type of TCI algorithm to be used. Options are "plasma" and "effect". Defaults to "effect". Will be overwritten if ‘custom_alg‘ is non-null.
`custom_alg`	Custom TCI algorithm to overwrite default plasma- or effect-site targeting.
`resp_bounds`	Optional vector of two values indicating minimum and maximum values possible for the response.
`seed`	An integer used to initialize the random number generator.

Examples

```
pkmod_prior <- pkmod(pars_pk = c(cl = 10, q2 = 2, q3 =20, v = 15, v2 = 30, v3 = 50, ke0 = 1.2))
pkmod_true  <- pkmod(pars_pk = c(cl = 16, q2 = 4, q3 =10, v = 20, v2 = 20, v3 = 80, ke0 = 0.8),
sigma_add = 0.1, log_response = TRUE)
target_vals <- c(2,3,4,3,3)
target_tms <- c(0,5,10,36,60)
obs_tms <- c(1,2,4,8,12,16,24,36,48)
sim <- olc(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms)
len <- 500
tms <- seq(0,60,length.out = len)
df <- data.frame(time = rep(tms,2),
                 value = c(predict(pkmod_true, sim$inf,tms)[,1],
                 predict(pkmod_prior, sim$inf,tms)[,1]),
                 type = c(rep("true",len),rep("prior",len)))
library(ggplot2)
ggplot(df, aes(x = time, y = value, color = type)) +
  geom_step(data = data.frame(time = target_tms, value = target_vals),
  aes(x = time, y = value), inherit.aes = FALSE) +
  geom_line() +
  geom_point(data = sim$obs, aes(x = time, y = obs), inherit.aes = FALSE)
```

---

pkmod *Create a pkmod object*

Description

User function to create pkmod objects with validation checks. Multiple rows are permitted for arguments ‘pars_pk‘, ‘pars_pd‘, ‘init‘

Usage

```
pkmod(
  pars_pk = NULL,
  init = NULL,
  pkfn = NULL,
  pars_pd = NULL,
  pdfn = NULL,
  pdinv = NULL,
  pcmpt = NULL,
  ecmpt = NULL,
  sigma_add = 0,
  sigma_mult = 0,
  log_response = FALSE,
  Omega = NULL
)
```

Arguments

pars_pk	Vector or matrix of named PK parameters. If not specified, the pkmod function will be inferred from the parameter names. Print 'list_parnms()' for acceptable parameter names.
init	Vector of initial concentrations. Will default to values of zero in all compartments if not specified.
pkfn	PK model function. Functions provided in 'tci' include 'pkmod1cpt', 'pkmod2cpt', 'pkmod3cpt', and 'pkmod3cptm'. User-defined functions should be specified here.
pars_pd	PD model parameters if a PD model is specified
pdfn	PD model function
pdinv	Inverse PD model function for use in TCI algorithms
pcmpt	Index of plasma compartment. Defaults to first compartment if not specified.
ecmpt	Index of effect-site compartment if a PD model is specified. Will default to last compartment if unspecified.
sigma_add	Standard deviation of additive residual error
sigma_mult	Standard deviation of multiplicative residual error
log_response	Logical value indicating if the response should be logged prior to adding error.
Omega	Optional matrix of random effect parameters. Column names should correspond to names of pars_pk, pars_pd, and sigma_add or sigma_mult.

Value

Returns a list with class "pkmod" if validation checks are passed. Returns an error if not.

Examples

```
# 1-compartment model
pkmod(pars_pk = c(CL = 10, V1 = 10))
# 2-compartment model
pkmod(pars_pk = c(CL = 10, V1 = 10, Q = 3, v2 = 20))
# 2-compartment model with random effects matrix
Omega <- matrix(diag(c(0.3,0.2,0,0.4)), 4,4, dimnames = list(NULL,c("CL","V1","Q","v2")))
pkmod(pars_pk = c(CL = 10, V1 = 10, Q = 3, v2 = 20), Omega = Omega)
```

---

pkmod1cpt *One compartment IV infusion with first-order elimination.*

Description

One compartment IV infusion with first-order elimination.

Usage

```
pkmod1cpt(tm, kR, pars, init = 0)
```

Arguments

tm	Vector of times to evaluate the PK function at
kR	Infusion rate (e.g. ml/min).
pars	Named vector of parameters with names ('k10','v1') or ('cl','v1').
init	Initial concentration. Defaults to 0.

Value

Numeric vector of concentrations for a constant infusion rate

Examples

```
pkmod1cpt(1,1,c(k10 = 0.5, v1 = 1))
pkmod1cpt(1,1,c(KE = 0.5, v1 = 1))
pkmod1cpt(1,1,c(CL = 0.5, v1 = 1))
```

---

pkmod2cpt *Two compartment IV infusion with first-order elimination.*

Description

Two compartment IV infusion with first-order elimination. Elimination from peripheral compartment is assumed to be zero unless 'k20' is specified.

Usage

```
pkmod2cpt(tm, kR, pars, init = c(0, 0))
```

Arguments

tm	Vector of times to evaluate the PK function at
kR	Infusion rate (e.g. ml/min).
pars	Named vector of parameters with names ('K10','K12','K21','V1','V2') or ('CL','Q','V1','V2').
init	Initial concentration. Defaults to 0 in both compartments.

Value

Numeric matrix of concentrations for a constant infusion rate

Examples

```
pkmod2cpt(1,1,c(CL = 15, V1 = 10, Q2 = 10, V2 = 20))
pkmod2cpt(1,1,c(CL = 15, v1 = 10, Q2 = 10, V2 = 20, cl2 = 4))
```

pkmod3cpt *Three compartment IV infusion with first-order elimination.*

Description

Three compartment IV infusion with first-order elimination. Elimination is assumed to occur only from central compartment if 'k20', 'k30' are not specified.

Usage

```
pkmod3cpt(tm, kR, pars, init = c(0, 0, 0))
```

Arguments

tm	Vector of times to evaluate the PK function at
kR	Infusion rate (e.g. ml/min).
pars	Named vector of parameters with names ('K10','K12','K21','V1','V2') or ('CL','Q','V1','V2').
init	Initial concentration. Defaults to 0 in all compartments.

Value

Numeric matrix of concentrations for a constant infusion rate

Examples

```
pkmod3cpt(1,1,c(CL = 15, Q2 = 10, Q3 = 5, V1 = 10, V2 = 20, V3 = 50))
```

pkmod3cptm *Solution to three-compartment IV model with effect-site*

Description

3 compartment IV infusion with first-order absorption between compartments and with an additional effect-site compartment. The analytical solutions implemented in this function are provided in "ADVAN-style analytical solutions for common pharmacokinetic models" by Abuhelwa et al. 2015.

Usage

```
pkmod3cptm(tm, kR, pars, init = c(0, 0, 0, 0))
```

Arguments

tm	Vector of times to evaluate the PK function at
kR	Infusion rate (e.g. ml/min).
pars	Named vector of parameters with names (k10,k12,k21,k13,k31,v1,v2,v3,ke0)
init	Initial concentration

Details

This function takes in arguments for each of the absorption and elimination rate constants of a three-compartment model as well as initial concentrations, c0. ke0 gives the rate of elimination from the effect-site compartment into the central compartment (i.e. k41). The rate of absorption into the effect-site compartment is set at 1/10,000 the value of ke0. The function returns a set of functions that calculate the concentration in each of the four compartments as a function of time.

Value

Numeric matrix of concentrations for a constant infusion rate

Examples

```
pars_3cpt <- c(k10=1.5,k12=0.15,k21=0.09,k13=0.8,k31=0.8,v1=10,v2=15,v3=100,ke0=1)
pkmod3cptm(1,1,pars_3cpt)
```

---

pkmod_eleveld_ppf *Eleveld population PK model for propofol*

Description

Function takes patient covariate values required for the Eleveld PK or PK-PD model for propofol and returns a ‘pkmod‘ object with the appropriate model parameters.

Usage

```
pkmod_eleveld_ppf(
  AGE,
  TBW,
  HGT,
  MALE,
  OPIATE = TRUE,
  ARTERIAL = TRUE,
  PMA = NULL,
  PD = TRUE,
  ...
)
```

Arguments

AGE	Age (years)
TBW	Weight (kg)
HGT	Height (cm)
MALE	Sex, logical
OPIATE	Logical indicating presence of opiates. Defaults to TRUE.
ARTERIAL	PK based on arterial sampling rather than venous. Defaults to TRUE.
PMA	Post-menstrual age. Calculated as AGE + 40 weeks if not provided.
PD	Logical. Should PD parameters be returned in addition to PK parameters.
...	Arguments passed to 'pkmod'

Value

'pkmod' object with Eleveld propofol population PK or PK-PD parameters

Examples

```
pkmod_eleveld_ppf(AGE = 40,TBW = 56,HGT=150,MALE = TRUE)
```

---

pkmod_eleveld_remi *Eleveld population PK model for remifentanil*

Description

Function takes patient covariate values required for the Eleveld PK or PK-PD model for propofol and returns a 'pkmod' object with the appropriate model parameters.

Usage

```
pkmod_eleveld_remi(AGE, MALE, TBW, HGT = NULL, BMI = NULL, PD = TRUE, ...)
```

Arguments

AGE	Age (years)
MALE	Sex, logical
TBW	Total body weight (kg).
HGT	Height (cm). Used to calculate BMI if not provided.
BMI	Body mass index
PD	Logical. Should PD parameters be returned in addition to PK parameters.
...	Arguments passed to 'pkmod'

Value

'pkmod' object with Eleveld remifentanil population PK or PK-PD parameters

Examples

```
pkmod_eleveld_remi(AGE = 40,TBW = 56,HGT=150,MALE = TRUE)
```

---

pkmod_kim *Kim population PK model for remifentanil*

Description

Evaluate Kim population PK model at patient covariate values. Published in Kim et al. (2017). "Disposition of Remifentanil in Obesity: A New Pharmacokinetic Model Incorporating the Influence of Body Mass" Anesthesiology Vol. 126, 1019–1032. doi: https://doi.org/10.1097/ALN.0000000000001635

Usage

```
pkmod_kim(AGE, TBW, HGT = NULL, BMI = NULL, MALE = NULL, FFM = NULL, ...)
```

Arguments

AGE	Age (years)
TBW	Total body weight (kg).
HGT	Height (cm). Used to calculate BMI if BMI is not provided.
BMI	Body mass index. Used to calculate LBM if LBM is not provided.
MALE	Logical. Used to calculate LBM if LBM is not provided.
FFM	Fat-free mass. Can be used instead of BMI and MALE.
...	Arguments passed to ‘pkmod‘

Value

‘pkmod‘ object with Schnider population PK parameters

Examples

```
pkmod_kim(AGE = 40,TBW = 75, BMI = 30, MALE = TRUE)
pkmod_kim(AGE = 40,TBW = 75, FFM = 52.83)
```

pkmod_marsh *Population PK and PK-PD functions* - *Marsh population PK model for propofol*

Description

Evaluates the Marsh propofol model at patient covariates (total body mass) and returns a 'pkmod' object. KE0 parameter set to 1.2 in accordance with recommendations from Absalom et al., 2009 "Pharmacokinetic models for propofol- Defining and illuminating the devil in the detail."

Usage

```
pkmod_marsh(TBW, ...)
```

Arguments

TBW	Weight (kg)
...	Arguments passed to 'pkmod'

Value

'pkmod' object with Marsh population PK parameters

Examples

```
pkmod_marsh(TBW = 50)
```

pkmod_minto *Minto population PK model for remifentanil*

Description

Evaluate Minto population PK model at patient covariate values. Published in Minto et al. (1997). "Influence of Age and Gender on the Pharmacokinetics and Pharmacodynamics of Remifentanil: I. Model Development." Anesthesiology 86:10-23 doi: https://doi.org/10.1097/00000542-199701000-00004. Residual error standard deviations are taken from Eleveld et al. (2017). "An Allometric Model of Remifentanil Pharmacokinetics and Pharmacodynamics." Anesthesiology Vol. 126, 1005–1018 doi: https://doi.org/10.1097/ALN.0000000000001634.

Usage

```
pkmod_minto(
  AGE,
  HGT = NULL,
  TBW = NULL,
  MALE = NULL,
  LBM = NULL,
  PD = TRUE,
  ...
)
```

Arguments

AGE	Age (years)
HGT	Height (cm). Used to calculate LBM if LBM is not provided.
TBW	Weight (kg). Used to calculate LBM if LBM is not provided.
MALE	Logical. Used to calculate LBM if LBM is not provided.
LBM	Lean body mass (kg). Can be provided instead of TBW, HGT, and MALE
PD	Logical. Should PD parameters be returned in addition to PK parameters.
...	Arguments passed to ‘pkmod‘

Value

‘pkmod‘ object with Schnider population PK parameters

Examples

```
pkmod_minto(AGE = 40,HGT=170,LBM = 43.9)
pkmod_minto(AGE = 40,HGT=170,TBW=50,MALE=TRUE)
```

---

pkmod_schnider *Schnider population PK model for propofol*

Description

Evaluate Schnider population PK model at patient covariate values. Published in Schnider et al. (1998). "The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers." Anesthesiology 88 (5):1170-82.

Usage

```
pkmod_schnider(AGE, HGT, LBM = NULL, TBW = NULL, MALE = NULL, ...)
```

Arguments

AGE	Age (years)
HGT	Height (cm)
LBM	Lean body mass (kg). Can be provided instead of TBW, and MALE
TBW	Weight (kg). Used to calculate LBM if LBM is not provided.
MALE	Logical. Used to calculate LBM if LBM is not provided.
...	Arguments passed to ‘pkmod‘

Value

‘pkmod‘ object with Schnider population PK parameters

Examples

```
pkmod_schnider(AGE = 40,HGT=170,LBM = 43.9)
pkmod_schnider(AGE = 40,HGT=170,TBW=50,MALE=TRUE)
```

---

plot.sim_tci *Plot method for sim_tci class*

Description

Plot object with class "sim_tci" created by ‘simulate_tci()‘.

Usage

```
## S3 method for class 'sim_tci'
plot(
  x,
  ...,
  yvar = NULL,
  id = NULL,
  type = c("true", "prior", "posterior"),
  show_inf = FALSE,
  show_data = FALSE,
  show_updates = FALSE,
  wrap_id = FALSE
)
```

Arguments

x	Object with class "sim_tci" created by ‘simulate_tci()‘
...	Other arguments. Not currently used.
yvar	Response variable. Options are concentrations ("c1","c2",...) or "pdresp" for a PD response. Only one variable may be plotted at a time.

id	Subset of IDs to plot. Will default to all if unspecified. Can be displayed in separate plots via ‘wrap_id‘ argument.
type	Type of response to plot. Options are "prior", "true", or "posterior" if closed-loop control was used.
show_inf	Logical. Display infusion rates alongside response values.
show_data	Logical. Display simulated data values in addition to responses.
show_updates	Logical, for closed-loop only. Show update times along x-axis.
wrap_id	Logical. Separate plots by ID value.

Value

Plots simulation results

Examples

```
data <- data.frame(ID = 1:2, AGE = c(30,40), TBW = c(70,80),
HGT = c(160,170), MALE = c(FALSE,TRUE))
pkmod_prior <- poppkmod(data, drug = "ppf", model = "eleveld")
pkmod_true  <- poppkmod(data, drug = "ppf", model = "eleveld", sample = TRUE)
obs_tms <- seq(1/6,10,1/6)
target_vals = c(75,60,50,50)
target_tms = c(0,3,6,10)

# open-loop simulation (without update_tms)
sim_ol <- simulate_tci(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms,
seed = 200)
plot(sim_ol, id = 1, type = "true")
plot(sim_ol, yvar = "c4", type = "true")
plot(sim_ol, yvar = "c4", type = "true", wrap_id = TRUE, show_inf = TRUE)

# closed-loop simulation (with update_tms)
## Not run:
sim_cl <- simulate_tci(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms,
update_tms = c(2,4,6), seed = 200)
plot(sim_cl, type = "posterior", id = 1, show_inf = TRUE)
plot(sim_cl, type = "posterior", wrap_id = TRUE, show_data = TRUE)
plot(sim_cl, yvar = "c4", wrap_id = TRUE)

## End(Not run)
```

---

poppkmod *Implement a population pharmacokinetic/pharmacodynamic model.*

Description

Create a ‘poppkmod‘ object using an existing population PK model for propofol or remifentanil using patient covariates. Available models for propofol are the Marsh, Schnider, and Eleveld models. Available models for remifentanil are the Minto, Kim, and Eleveld models. Input is a data frame with rows corresponding to individuals and columns recording patient covariates. An ID column is optional, but will be generated as 1:nrow(data) if not supplied. Covariates required by each model are

Propofol

- Marsh: TBW
- Schnider: (AGE, HGT, TBW, MALE) or (AGE, HGT, LBW)
- Eleveld: AGE, TBW, HGT, MALE

Remifentanil

- Minto: (AGE, HGT, TBW, MALE) or (AGE, HGT, LBW)
- Kim: (AGE, TBW, BMI, HGT) or (AGE, TBW, FFM)
- Eleveld: (AGE, MALE, TBW, HGT) or (AGE, MALE, TBW, BMI)

Abbreviations

- TBW = Total body weight (kg)
- LBW = Lean body weight (kg)
- FFM = Fat-free mass (kg)
- AGE = Age (years)
- HGT = Height (cm)
- MALE = Male (1/0, TRUE/FALSE)
- BMI = Body mass index (kg/m^2)

Usage

```
poppkmod(
  data,
  drug = c("ppf", "remi"),
  model = c("marsh", "schnider", "eleveld", "minto", "kim"),
  sample = FALSE,
  PD = TRUE,
  ...
)
```

Arguments

data	Data frame of patient covariates. ID values, if used, should be in a column labeled "id" or "ID"
drug	"ppf" for propofol or "remi" for remifentanil. Defaults to "ppf".

model	Model name. Options are "marsh", "schnider", or "eleveld" if drug = "ppf", or "minto", "kim", or "eleveld" if drug = "remi".
sample	Logical. Should parameter values be sampled from interindividual distribution (TRUE) or evaluated at point estimates for covariates (FALSE)? Defaults to FALSE.
PD	Logical. If applicable, should the PD component be evaluated for PK-PD models. Defaults to TRUE.
...	Arguments passed on to each pkmod object

Value

'poppkmod' object

Examples

```
data <- data.frame(ID = 1:5, AGE = seq(20,60,by=10), TBW = seq(60,80,by=5),
HGT = seq(150,190,by=10), MALE = c(TRUE,TRUE,FALSE,FALSE,FALSE))
poppkmod(data, drug = "ppf", model = "eleveld")
poppkmod(data, drug = "remi", model = "kim")
```

---

predict.pkmod *Predict method for pkmod objects*

Description

Predict concentrations from a pkmod object - can be a user defined function

Usage

```
## S3 method for class 'pkmod'
predict(object, inf, tms, return_times = FALSE, ...)
```

Arguments

object	An object with class pkmod.
inf	A matrix with columns "begin","end","inf_rate" indicating when infusions should be administered. Can be created by 'inf_manual' or 'inf_tci'.
tms	Times at which to calculate predicted concentrations.
return_times	Logical. Should prediction times be returned along with responses? Defaults to FALSE.
...	List or vector of values to be passed on to update.pkmod.

Value

Matrix of predicted concentrations associated with a pkmod object and and infusion schedule.

Examples

```
# dosing schedule
dose <- inf_manual(inf_tms = c(0,0.5,4,4.5,10), inf_rate = c(100,0,80,0,0))
# pkmod object
my_mod <- pkmod(pars_pk = c(CL = 15, V1 = 10, Q2 = 10, V2 = 20))
# predict at specific times
predict(my_mod, inf = dose, tms = c(1.5,2.5,3))
# predict with an Emax PD function
my_mod_pd <- pkmod(pars_pk = c(v1 = 8.995, v2 = 17.297, v3 = 120.963, cl = 1.382,
q2 = 0.919, q3 = 0.609, ke0 = 1.289),
pars_pd = c(c50 = 2.8, gamma = 1.47, gamma2 = 1.89, e0 = 93, emx = 93),
pdfn = emax, pdinv = emax_inv, ecmpt = 4)
predict(my_mod_pd, inf = dose, tms = c(1.5,2.5,3))
# predict with a subset of new PK-PD parameters
predict(my_mod_pd, inf = dose, tms = c(1.5,2.5,3), pars_pk = c(ke0 = 0.8),
pars_pd = c(c50 = 2, e0 = 100))
```

---

predict.poppkmod *Predict method for pkmod objects*

Description

Predict concentrations from a pkmod object - can be a user defined function

Usage

```
## S3 method for class 'poppkmod'
predict(object, inf, tms, ...)
```

Arguments

object	An object with class poppkmod.
inf	A matrix with columns "begin","end","inf_rate" indicating when infusions should be administered. Can be created by ‘inf_manual‘ or ‘inf_tci‘.
tms	Times at which to calculate predicted concentrations.
...	List or vector of values to be passed on to predict.pkmod.

Value

Matrix of predicted concentrations associated with a poppkmod object and and infusion schedule.

Examples

```
# dosing schedule
dose <- inf_manual(inf_tms = c(0,0.5,4,4.5,10), inf_rate = c(100,0,80,0,0))
# poppkmod object
data <- data.frame(ID = 1:5, AGE = seq(20,60,by=10), TBW = seq(60,80,by=5),
HGT = seq(150,190,by=10), MALE = c(TRUE,TRUE,FALSE,FALSE,FALSE))
```

```
elvd_mod <- poppkmod(data, drug = "ppf", model = "eleveld")
predict(elvd_mod, inf = dose, tms = c(1.5,2.5,3))
```

`print.pkmod` *Print pkmod*

Description

Print method for pkmod objects

Usage

```
## S3 method for class 'pkmod'
print(x, ..., digits = 3)
```

Arguments

`x`	Object with class "pkmod" created by ‘pkmod()‘
`...`	Arguments passed to ‘update.pkmod()‘
`digits`	Number of significant digits to print

Value

Prints description of pkmod

Examples

```
# 1-parameter model
pkmod(pars_pk = c(CL = 10, V1 = 10))
```

`print.poppkmod` *Print poppkmod*

Description

Print method for poppkmod objects

Usage

```
## S3 method for class 'poppkmod'
print(x, ..., digits = 3)
```

Arguments

`x`	Object with class "pkmod" created by ‘poppkmod()‘
`...`	Additional arguments. Not used
`digits`	Number of significant digits to print

Value

Prints description of pkmod

Examples

```
data <- data.frame(ID = 1:5,
AGE = seq(20,60,by=10),
TBW = seq(60,80,by=5),
HGT = seq(150,190,by=10),
MALE = c(TRUE,TRUE,FALSE,FALSE,FALSE))
poppkmod(data, drug = "ppf", model = "eleveld")
poppkmod(data, drug = "remi", model = "kim")
```

---

print.sim_tci *Print method for sim_tci class*

Description

Print object with class "sim_tci" created by ‘simulate_tci()‘.

Usage

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

Arguments

x	Object with class "sim_tci" created by ‘simulate_tci()‘
...	Other arguments. Not currently used.

Value

Prints a description of the simulation.

Examples

```
data <- data.frame(ID = 1:3, AGE = c(20,30,40), TBW = c(60,70,80),
HGT = c(150,160,170), MALE = c(TRUE,FALSE,TRUE))
pkmod_prior <- poppkmod(data, drug = "ppf", model = "eleveld")
pkmod_true  <- poppkmod(data, drug = "ppf", model = "eleveld", sample = TRUE)
obs_tms <- seq(1/6,10,1/6)
target_vals = c(75,60,50,50)
target_tms = c(0,3,6,10)

# open-loop simulation (without update_tms)
sim_ol <- simulate_tci(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms,
seed = 200)

# closed-loop simulation (with update_tms)
```

```
## Not run:
sim_cl <- simulate_tci(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms,
update_tms = c(2,4,6,8), seed = 200)

## End(Not run)
```

`sample_iiv` *Sample PK or PK-PD parameters from the distribution of inter- or intra-individual variability*

Description

Sample PK or PK-PD parameters from the distribution of random effects for a ‘pkmod‘ or ‘poppkmod‘ object, as described by the Omega matrix (see ?pkmod).

Usage

```
sample_iiv(mod, log_normal = TRUE, ...)
```

Arguments

`mod`	‘pkmod‘ or ‘poppkmod‘ object with associated Omega matrix describing random effect variances
`log_normal`	Logical. Assumes random effects are log-normally distributed and multiplicative if TRUE, additive and normally distributed if FALSE.
`...`	Arguments passed to update.pkmod.

Value

Returns model passed to "mod" argument with randomly sampled PK or PK-PD parameters.

Examples

```
# sample from single PK model
sample_iiv(pkmod_schnider(AGE = 40,HGT=170,TBW=50,MALE=TRUE))
# sample from `poppkmod`
data <- data.frame(ID = 1:5, AGE = seq(20,60,by=10), TBW = seq(60,80,by=5),
HGT = seq(150,190,by=10), MALE = c(TRUE,TRUE,FALSE,FALSE,FALSE))
sample_iiv(poppkmod(data = data, drug = "ppf", model = "eleveld"))
```

sample_pkmod *Sample parameters from a 'pkmod' object*

Description

Sample parameters from a 'pkmod' object

Usage

```
sample_pkmod(pkmod, log_normal = TRUE, ...)
```

Arguments

pkmod	'pkmod' object with associated Omega matrix describing random effect variances
log_normal	Logical. Assumes random effects are log-normally distributed and multiplicative if TRUE, additive and normally distributed if FALSE.
...	Arguments passed to update.pkmod

Value

'pkmod' object with updated parameters.

Examples

```
sample_pkmod(pkmod_schnider(AGE = 40,HGT=170,TBW=50,MALE=TRUE))
sample_pkmod(pkmod_eleveld_ppf(AGE = 40,TBW = 56,HGT=150,MALE = TRUE, PD = FALSE))
```

simulate.pkmod *Simulate method for pkmod objects*

Description

Simulate observations from a pkmod object

Usage

```
## S3 method for class 'pkmod'
simulate(
  object,
  nsim = 1,
  seed = NULL,
  ...,
  inf,
  tms,
  obs_cmpt = 1,
  resp_bounds = NULL
)
```

Arguments

object	An object with class "pkmod" generated by ‘pkmod‘
nsim	Number of observations to simulate at each time point. Defaults to 1.
seed	An integer used to initialize the random number generator.
...	Arguments passed to ‘update.pkmod‘.
inf	A matrix of infusion rates with columns ’begin’, ’end’, and ’inf_rate’. This can be created manually, by ‘inf_manual‘, or by ‘inf_tci‘.
tms	Times at which to simulate observations.
obs_cmpt	Integer value indicating compartment in which observations are taken. Overridden if a PD model is included.
resp_bounds	Optional vector of two values indicating minimum and maximum values possible for the response.

Examples

```
# simulate data from a 2 compartment model with multiplicative error
dose <- inf_manual(inf_tms = c(0,0.5,4,4.5,10), inf_rate = c(100,0,80,0,0))
my_mod <- pkmod(pars_pk = c(CL = 10, V1 = 10, Q2 = 4, V2 = 30))
inf <- inf_tci(my_mod, target_vals = c(2,3,4,4), target_tms = c(0,2,3,10), "plasma")
simulate(my_mod, nsim = 3, inf = inf, tms = c(1,2,4,6,10), sigma_mult = 0.2)
# simulate with PD model
my_mod_pd <- pkmod(pars_pk = c(v1 = 8.995, v2 = 17.297, v3 = 120.963, cl = 1.382,
q2 = 0.919, q3 = 0.609, ke0 = 1.289),
pars_pd = c(c50 = 2.8, gamma = 1.47, gamma2 = 1.89, e0 = 93, emx = 93),
pdfn = emax, pdinv = emax_inv, ecmpt = 4)
simulate(my_mod_pd, inf = dose, tms = c(1.5,2.5,3))
```

---

simulate.poppkmod *Summary method for ‘poppkmod‘ objects*

Description

Summarize parameter distribution Simulate method for poppkmod objects

Usage

```
## S3 method for class 'poppkmod'
simulate(
  object,
  nsim = 1,
  seed = NULL,
  ...,
  inf,
  tms,
  obs_cmpt = 1,
  resp_bounds = NULL
)
```

Arguments

object	An object with class "poppkmod" generated by ‘poppkmod‘
nsim	Number of observations to simulate at each time point. Defaults to 1.
seed	An integer used to initialize the random number generator.
...	Arguments passed to ‘update.pkmod‘.
inf	A matrix of infusion rates with columns ’begin’, ’end’, and ’inf_rate’. This can be created manually, by ‘inf_manual‘, or by ‘inf_tci‘.
tms	Times at which to simulate observations.
obs_cmpt	Integer value indicating compartment in which observations are taken. Overridden if a PD model is included.
resp_bounds	Optional vector of two values indicating minimum and maximum values possible for the response.

Details

Simulate observations from a poppkmod object

Examples

```
# simulate data from a 2 compartment model with multiplicative error
dose <- inf_manual(inf_tms = c(0,0.5,4,4.5,10), inf_rate = c(100,0,80,0,0))
# poppkmod object
data <- data.frame(ID = 1:5, AGE = seq(20,60,by=10), TBW = seq(60,80,by=5),
 HGT = seq(150,190,by=10), MALE = c(TRUE,TRUE,FALSE,FALSE,FALSE))
elvd_mod <- poppkmod(data, drug = "ppf", model = "eleveld")
inf <- inf_tci(elvd_mod, target_vals = c(2,3,4,4), target_tms = c(0,2,3,10), "plasma")
simulate(elvd_mod, nsim = 3, inf = inf, tms = c(1,2,4,6,10))
```

---

simulate_clc *Simulate closed-loop control using Bayesian updates*

Description

Simulate closed-loop control using Bayesian updates for ‘pkmod‘ or ‘poppkmod‘ objects. Infusion rates are calculated using ‘pkmod_prior‘ to reach ‘target_vals‘ at ‘target_tms‘. Data values are simulated using ‘pkmod_true‘ at ‘obs_tms‘. ‘pkmod_prior‘ and ‘pkmod_true‘ do not need to have the same structure. Model parameters are updated at each update time using all available simulated observations. Processing delays can be added through the ‘delay‘ argument, such that observations aren’t made available to the update mechanism until ‘update_tms >= obs_tms + delay‘.

Usage

```
simulate_clc(
  pkmod_prior,
  pkmod_true,
  target_vals,
  target_tms,
  obs_tms,
  update_tms,
  type = c("effect", "plasma"),
  custom_alg = NULL,
  resp_bounds = NULL,
  delay = 0,
  seed = NULL,
  verbose = TRUE
)
```

Arguments

pkmod_prior	‘pkmod‘ or ‘poppkmod‘ object describing a PK/PK-PD model that is used to calculate TCI infusion rates and is updated as data are simulated and incorporated. Must have an associated Omega matrix.
pkmod_true	‘pkmod‘ or ‘poppkmod‘ object describing the patient’s "true" response. This model will be used to simulate observations.
target_vals	A vector of numeric values indicating PK or PD targets for TCI algorithm.
target_tms	A vector of numeric values indicating times at which the TCI algorithm should begin targeting each value.
obs_tms	Times at which data values should be simulated from ‘pkmod_true‘.
update_tms	Times at which ‘pkmod_prior‘ should be updated using all available simulated observations.
type	Type of TCI algorithm to be used. Options are "plasma" and "effect". Defaults to "effect". Will be overwritten if ‘custom_alg‘ is non-null.
custom_alg	Custom TCI algorithm to overwrite default plasma- or effect-site targeting.
resp_bounds	Optional vector of two values indicating minimum and maximum values possible for the response.
delay	Optional numeric value indicating a temporal delay between when observations are simulated and when they should be made available for updating ‘pkmod_prior‘. For example, a delay should be set to account for a processing time delay in Bispectral Index measurements or the time required to measure drug concentrations from collected samples.
seed	An integer used to initialize the random number generator.
verbose	Logical. Print progress as simulation is run.

Examples

```
data <- data.frame(ID = 1:3, AGE = c(20,30,40), TBW = c(60,70,80),
```

```
HGT = c(150,160,170), MALE = c(TRUE,FALSE,TRUE))
pkmod_prior <- poppkmod(data, drug = "ppf", model = "eleveld")
pkmod_true  <- poppkmod(data, drug = "ppf", model = "eleveld", sample = TRUE)
obs_tms <- seq(1/6,10,1/6)
update_tms <- c(2,4,6,8)
target_vals = c(75,60,50,50)
target_tms = c(0,3,6,10)
## Not run:
sim <- simulate_clc(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms,
update_tms, seed = 200)
len <- 500
tms <- seq(0,10,length.out = len)
resp <- data.frame(rbind(predict(pkmod_true, sim$inf, tms),
predict(pkmod_prior, sim$inf, tms),
predict(sim$pkmod_post, sim$inf, tms)))
resp$type = c(rep("true",len*3),rep("prior",len*3),rep("posterior",len*3))
library(ggplot2)
ggplot(resp) + geom_line(aes(x = time, y = pdresp, color = factor(id))) +
facet_wrap(~type) + labs(x = "Hours", y = "Bispectral Index") +
  geom_step(data = data.frame(time = target_tms, value = target_vals),
  aes(x = time, y = value), inherit.aes = FALSE)

## End(Not run)
```

`simulate_olc` *Simulate open-loop control using TCI*

Description

Simulate open-loop control using TCI for ‘pkmod‘ or ‘poppkmod‘ objects. Infusion rates are calculated using ‘pkmod_prior‘ to reach ‘target_vals‘ at ‘target_tms‘. Data values are simulated using ‘pkmod_true‘ at ‘obs_tms‘. ‘pkmod_prior‘ and ‘pkmod_true‘ do not need to have the same structure, but are required to have the same number of IDs (i.e., N) if ‘poppkmod‘ objects are used.

Usage

```
simulate_olc(
  pkmod_prior,
  pkmod_true,
  target_vals,
  target_tms,
  obs_tms,
  type = c("effect", "plasma"),
  custom_alg = NULL,
  resp_bounds = NULL,
  seed = NULL
)
```

Arguments

pkmod_prior	‘pkmod‘ object describing a PK/PK-PD model that is used to calculate TCI infusion rates and is updated as data are simulated and incorporated. Must have an associated Omega matrix.
pkmod_true	‘pkmod‘ object describing the patient’s "true" response. This model will be used to simulate observations.
target_vals	A vector of numeric values indicating PK or PD targets for TCI algorithm.
target_tms	A vector of numeric values indicating times at which the TCI algorithm should begin targeting each value.
obs_tms	Times at which data values should be simulated from ‘pkmod_true‘.
type	Type of TCI algorithm to be used. Options are "plasma" and "effect". Defaults to "effect". Will be overwritten if ‘custom_alg‘ is non-null.
custom_alg	Custom TCI algorithm to overwrite default plasma- or effect-site targeting.
resp_bounds	Optional vector of two values indicating minimum and maximum values possible for the response.
seed	An integer used to initialize the random number generator.

Examples

```
data <- data.frame(ID = 1:5, AGE = seq(20,60,by=10), TBW = seq(60,80,by=5),
HGT = seq(150,190,by=10), MALE = c(TRUE,TRUE,FALSE,FALSE,FALSE))
pkmod_prior <- poppkmod(data, drug = "ppf", model = "eleveld")
pkmod_true  <- poppkmod(data, drug = "ppf", model = "eleveld", sample = TRUE)
obs_tms <- seq(1/6,10,1/6)
target_vals = c(75,60,50,50)
target_tms = c(0,3,6,10)
sim <- simulate_olc(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms)
len <- 500
tms <- seq(0,10,length.out = len)
resp <- data.frame(rbind(predict(pkmod_true, sim$inf, tms),
predict(pkmod_prior, sim$inf, tms)))
resp$type = c(rep("true",len*5),rep("prior",len*5))
library(ggplot2)
ggplot(resp) + geom_line(aes(x = time, y = pdresp, color = factor(id))) + facet_wrap(~type) +
  labs(x = "Hours", y = "Bispectral Index") + theme_bw() +
  geom_step(data = data.frame(time = target_tms, value = target_vals),
  aes(x = time, y = value), inherit.aes = FALSE)
```

---

simulate_tci *Simulate open- or closed-loop control*

Description

Simulate responses from a ‘pkmod‘ or ‘poppkmod‘ object using TCI control. Infusion rates are calculated to reach targets using ‘pkmod_prior‘. Data values are simulated using ‘pkmod_true‘. ‘pkmod_prior‘ and ‘pkmod_true‘ do not need to have the same parameters or structure and should be different when simulating responses under model misspecification. If update times (argument ‘update_tms‘) are provided then the function ‘simulate_clc‘ is called for "closed-loop" control and model parameters will be updated via Bayes' rule using available data. Only parameters with values in the Omega matrix will be updated. A data processing delay can be added through the argument ‘delay‘. See ?bayes_update? for more details. If update times are not specified, then the function ‘simulate_olc‘ will be called to implement "open-loop" control and model parameters will not be updated. Simulation results have class ‘tci_sim‘ and can be plotted using ‘plot.tci_sim()‘.

Usage

```
simulate_tci(
  pkmod_prior,
  pkmod_true,
  target_vals,
  target_tms,
  obs_tms,
  update_tms = NULL,
  type = c("effect", "plasma"),
  custom_alg = NULL,
  resp_bounds = NULL,
  delay = 0,
  seed = NULL,
  verbose = TRUE
)
```

Arguments

pkmod_prior	‘pkmod‘ or ‘poppkmod‘ object describing a PK/PK-PD model that is used to calculate TCI infusion rates and is updated as data are simulated and incorporated. Must have an associated Omega matrix.
pkmod_true	‘pkmod‘ or ‘poppkmod‘ object describing the patient's "true" response. This model will be used to simulate observations.
target_vals	A vector of numeric values indicating PK or PD targets for TCI algorithm.
target_tms	A vector of numeric values indicating times at which the TCI algorithm should begin targeting each value.
obs_tms	Times at which data values should be simulated from ‘pkmod_true‘.
update_tms	Times at which ‘pkmod_prior‘ should be updated using all available simulated observations.
type	Type of TCI algorithm to be used. Options are "plasma" and "effect". Defaults to "effect". Will be overwritten if ‘custom_alg‘ is non-null.
custom_alg	Custom TCI algorithm to overwrite default plasma- or effect-site targeting.

resp_bounds	Optional vector of two values indicating minimum and maximum values possible for the response.
delay	Optional numeric value indicating a temporal delay between when observations are simulated and when they should be made available for updating 'pkmod_prior'. For example, a delay should be set to account for a processing time delay in Bispectral Index measurements or the time required to measure drug concentrations from collected samples.
seed	An integer used to initialize the random number generator.
verbose	Logical. Print progress as simulation is run.

Examples

```
data <- data.frame(ID = 1:3, AGE = c(20,30,40), TBW = c(60,70,80),
HGT = c(150,160,170), MALE = c(TRUE,FALSE,TRUE))
pkmod_prior <- poppkmod(data, drug = "ppf", model = "eleveld")
pkmod_true  <- poppkmod(data, drug = "ppf", model = "eleveld", sample = TRUE)
obs_tms <- seq(1/6,10,1/6)
target_vals = c(75,60,50,50)
target_tms = c(0,3,6,10)

# open-loop simulation (without updates)
sim_ol <- simulate_tci(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms,
seed = 200)
plot(sim_ol)

# closed-loop simulation (with updates)
## Not run:
sim_cl <- simulate_tci(pkmod_prior, pkmod_true, target_vals, target_tms, obs_tms,
update_tms = c(2,4,6,8), seed = 200)
plot(sim_cl, wrap_id = TRUE, show_inf = TRUE, show_data = TRUE)

## End(Not run)
```

---

tci_documentation *tci_documentation*

Description

Functions to implement target-controlled infusion algorithms

Details

tci package documentation

This package contains functions to implement target-controlled infusion (TCI) algorithms for compartmental PK models under intravenous administration. TCI algorithms for plasma or effect-site targeting are included and can be extended to pharmacodynamic responses. Custom PK-PD models and custom TCI algorithms can be specified. Functions are provided to simulate responses from PK/PK-PD models under open- or closed-loop control.

`tci_effect` *Effect-site TCI algorithm with plasma targeting within small range of target*

Description

Modified effect-site TCI algorithm that switches to plasma-targeting when the plasma concentration is within 20% of the target and the effect-site concentration is within 0.5% of the target. The modification decreases computation time and prevents oscillatory behavior in the effect-site concentrations.

Usage

```
tci_effect(Ct, pkmod, dtm = 1/6, cptol = 0.2, cetol = 0.05, ...)
```

Arguments

`Ct`	Numeric vector of target effect-site concentrations.
`pkmod`	PK model
`dtm`	TCI update frequency. Defaults to 1/6, corresponding to 10-second intervals if model parameters are in terms of minutes.
`cptol`	Percentage of plasma concentration required to be within to switch to plasma targeting.
`cetol`	Percentage of effect-site concentration required to be within to switch to plasma targeting.
`...`	Arguments passed on to 'tci_plasma' and 'tci_effect_only' functions, including to update.pkmod.

Value

Numeric value

Examples

```
my_mod <- pkmod(pars_pk = c(v1 = 8.995, v2 = 17.297, v3 = 120.963, cl = 1.382,
q2 = 0.919, q3 = 0.609, ke0 = 1.289))
tci_effect(Ct = 2, pkmod = my_mod)
# update parameters
tci_effect(Ct = 2, pkmod = my_mod, pars_pk = c(v1 = 12, cl = 2))
```

`tci_effect_only` *TCI algorithm for effect-site targeting*

Description

Function for calculating a TCI infusion schedule corresponding to a set of target concentrations. This function makes use of formulas described by Shafer and Gregg (1992) in "Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer-controlled infusion pump"

Usage

```
tci_effect_only(
  Ct,
  pkmod,
  dtm = 1/6,
  tmax_search = 10,
  maxrt = 1200,
  grid_len = 1200,
  ...
)
```

Arguments

`Ct`	Numeric vector of target effect-site concentrations.
`pkmod`	PK model
`dtm`	Frequency of TCI updates. Default is 1/6 minutes = 10 seconds.
`tmax_search`	Outer bound on times searched to find a maximum concentration following an infusion of duration dtm. Defaults to 20 minutes. May need to be increased if a drug has a slow elimination rate.
`maxrt`	Maximum infusion rate of TCI pump. Defaults to 1200.
`grid_len`	Number of time points used to identify time of maximum concentration. Can be increased for more precision.
`...`	List or vector of named values to be passed on to update.pkmod.

Value

Numeric value

Examples

```
# three compartment model with effect site
my_mod <- pkmod(pars_pk = c(v1 = 8.995, v2 = 17.297, v3 = 120.963,
cl = 1.382, q2 = 0.919, q3 = 0.609, ke0 = 1.289))
tci_effect_only(Ct = 2, pkmod = my_mod)
# update parameters
tci_effect_only(Ct = 2, pkmod = my_mod, pars_pk = c(v1 = 12, cl = 2))
```

tci_plasma *TCI algorithm for plasma targeting*

Description

TCI algorithm based on the algorithm described by Jacobs (1990).

Usage

```
tci_plasma(Ct, pkmod, dtm = 1/6, maxrt = 1200, ...)
```

Arguments

Ct	Target plasma concentration
pkmod	PK model
dtm	Duration of the infusion
maxrt	Maximum infusion rate. Defaults to 200 ml/min in reference to the maximum infusion rate of 1200 ml/h permitted by existing TCI pumps (e.g. Anestfusor TCI program).
...	Arguments passed on to update.pkmod.

Value

Numeric value

Examples

```
# plasma targeting
my_mod <- pkmod(pars_pk = c(CL = 10, V1 = 10))
tci_plasma(Ct = 2, my_mod)
# update CL parameter
tci_plasma(Ct = 2, my_mod, pars_pk = c(CL = 15))
```

update.pkmod *Update method for pkmod*

Description

Update parameters or initial values of a pkmod object

Usage

```
## S3 method for class 'pkmod'
update(object, ...)
```

Arguments

object	Object with class pkmod
...	Updated values passed to object.

Value

Returns the pkmod object with elements replaced

Examples

```
# initial pkmod object
(my_mod <- pkmod(pars_pk = c(CL = 10, V1 = 10)))
# update a subset of parameters and initial values
update(my_mod, pars_pk = c(CL = 20, V1 = 2), init = 3, sigma_add = 1, log_response = TRUE)
```

---

validate_pkmod *pkmod validation checks*

Description

Function to provide validation checks for a pkmod object

Usage

```
validate_pkmod(x)
```

Arguments

x	Object of class "pkmod"

Value

Returns a list with class "pkmod" if validation checks are passed. Returns an error if not.

Examples

```
validate_pkmod(init_pkmod(pars_pk = c(CL = 10, V1 = 10,Q2 = 4,V2=20)))
```

validate_poppkmod *Perform validation checks on a ‘poppkmod‘ object*

Description

Perform validation checks on a ‘poppkmod‘ object created by ‘init_poppkmod‘.

Usage

```
validate_poppkmod(x)
```

Arguments

x	Object with class "poppkmod" created by init_poppkmod

Value

‘poppkmod‘ object or error

Examples

```
data <- data.frame(ID = 1:5, AGE = seq(20,60,by=10), TBW = seq(60,80,by=5),
HGT = seq(150,190,by=10), MALE = c(TRUE,TRUE,FALSE,FALSE,FALSE))
validate_poppkmod(init_poppkmod(data, drug = "ppf", model = "eleveld"))
```

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