Package 'breathtestcore'

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Title Core Functions to Read and Fit 13c Time Series from Breath Tests

Description Reads several formats of 13C data (IRIS/Wagner, BreathID) and CSV. Creates artificial sample data for testing. Fits Maes/Ghoos, Bluck-Coward self-correcting formula using 'nls', 'nlme'. Methods to fit breath test curves with Bayesian Stan methods are refactored to package 'breathteststan'. For a Shiny GUI, see package 'dmenne/breathtestshiny' on github.

License GPL-3

Version 0.8.0

URL https://github.com/dmenne/breathtestcore

BugReports https://github.com/dmenne/breathtestcore/issues

Depends R (>= 4.0.0)

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AIC.breathtestnlmefit S3 AIC method for breathtestnlmefit

Description

Extract AIC from a model fitted with nlme_fit

Usage

```
## S3 method for class 'breathtestnlmefit'
AIC(object, ...)
```

Arguments

object of class breathtestnlmefit

... not used

 ${\tt augment.breathtestfit} \ \ \textit{Augmented prediction for breathtest fit}$

Description

Broom method augment to compute predicted values from the results of class breathttestfit as generated by nls_fit or nlme_fit.

Usage

```
## S3 method for class 'breathtestfit'
augment(x, by = NULL, minute = NULL, dose = 100, ...)
```

Arguments

Χ	Object of class breathttestfit
by	When by is NULL, predictions for the original data values are returned. When by is a positive number, it is used as a step size for a sequence of minutes from 0 to the maximum value of minute in data set.
minute	When a vector is passed, this overrides settings in by, and predictions are calculated at the requested minute values.
dose	13C acetate or octanoate dose
	other parameters passed to methods

Value

When by is NULL, returns one row for each original observation pdr, and column fitted. If new data are given, i.e. when one of parameter by or minute is not null, only column fitted is added.

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See Also

augment

Examples

```
library(broom)
# Generate simulated data
data = cleanup_data(simulate_breathtest_data(n_records = 3)$data)
# Fit using the curves individually
fit = nls_fit(data)
# Predict values at t=60 and t=120
augment(fit, minute = c(60, 120))
```

breathtest_data

Data structure with PDR data and descriptors for breath test records

Description

Generates structure of class breathtest_data with required fields and optional fields. Optional fields by default are NA. This structure is used internally as an intermediate when reading in external file formats. All read_xxx functions return this structure, or a list of this structure (e.g. read_breathid_xml), and any converter to a new format should do the same to be used with cleanup_data. To support a new format with, also update breathtest_read_function which returns the most likely function to read the file by reading a few lines in it.

Usage

```
breathtest_data(
  patient_id,
  name = NA,
  first_name = NA,
  initials = NA,
  dob = NA,
  birth_year = NA,
  gender = NA,
  study = NA,
  pat_study_id = NA,
  file_name,
  device = "generic",
  substrate,
  record_date.
  start_time = record_date,
  end_time = record_date,
  test_no,
  dose = 100,
  height = 180,
```

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```
weight = 75,
t50 = NA,
gec = NA,
tlag = NA,
data = data
)
```

Arguments

patient_id required, string or number for unique identification

name optional first_name optional

initials optional, 2 characters, 1 number

dob optional date of birth (not to be confused with "delta over baseline")

birth_year optional

gender optional m or f

study optional name of study; can be used in population fit

pat_study_id optional; patient number within study_ does not need to be globally unique

file_name required; file where data were read from, or other unique string_ when data are

read again, this string is tested and record is skipped when same filename is already in database, therefore uniqueness is important_ when some record does not turn up in database after repeated reading, check if a record with the same

file name is already there, and rename the file to avoid collisions_

device breath id or iris; default "generic"

substrate should contain string "ace" or "oct" or "okt", case insensitive_ will be replaced

by "acetate" or "octanoate". If empty, "ocatanoate" is assumed.

record_date required record date_

start_time optional end_time optional

test_no required integer; unique test number converted to integer if factor

dose optional, default 100 mg

height optional, in cm; when pdr must be calculated, default values are used; see

dob_to_pdr

weight optional, in kg

optional, only present if device computes this value gec optional, only present if device computes this value tlag optional, only present if device computes this value

data frame with at least 5 rows and columns minute or time and one or both

of dob or pdr. If pdr is missing, and height, weight and substrate are given, computes pdr via function dob_to_pdr. When height and weight are missing,

defaults 180 cm and 75 kg are used instead.

Examples

```
# Read a file with known format
iris_csv_file = btcore_file("IrisCSV.TXT")
iris_csv_data = read_iris_csv(iris_csv_file)
# Note that many filds are NA
str(iris_csv_data)
# Convert to a format that can be fed to one of the fit functions
iris_df = cleanup_data(iris_csv_data)
# Individual curve fit
coef(nls_fit(iris_df))
```

breathtest_read_function

Snoop method to read breath test file

Description

Reads the first line of a file, and returns the best matching function to read the breath test data in it. To automatically read the file with the inferred file type, use read_any_breathtest. For Excel files, only the first sheet is read.

Usage

```
breathtest_read_function(filename = NULL, text = NULL)
```

Arguments

filename breath test data file from Iris/Wagner (extended or CSV), BreathID

text as alternative to filename, pass the text of the file directly. This parameter is not

used for Excel files.

Value

Function to read the file or the text; NULL if no matching function was found

```
file = btcore_file("IrisCSV.TXT")
# Get function to read this file. Returns \code{\link{read_iris_csv}}.
read_fun = breathtest_read_function(file)
str(read_fun(file))
# or, simple (returns a list!)
str(read_any_breathtest(file), 1)
```

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btcore_file

Path to example breath test data file

Description

Path to example breath test data file

Usage

```
btcore_file(filename = NULL, full.names = FALSE)
```

Arguments

filename example file in extdata directory without path. Case sensitive on Unix. When

filename is missing, returns the names of the available sample files.

full.names When filename is NULL, return full path names

Value

full filename to example file to use in read_xxx

Examples

```
head(btcore_file())
filename = btcore_file("IrisMulti.TXT")
data = read_iris(filename)
```

cleanup_data

Transforms 13C breath data into a clean format for fitting

Description

Accepts various data formats of ungrouped or grouped 13C breath test time series, and transforms these into a data frame that can be used by all fitting functions, e.g. nls_fit. If in doubt, pass data frame through cleanup_data before forwarding it to a fitting function. If the function cannot repair the format, it gives better error messages than the xxx_fit functions.

Usage

```
cleanup_data(data, ...)
```

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Arguments

data

- A data frame, array or tibble with at least two numeric columns with optional names minute and pdr to fit a single 13C record.
- A data frame or tibble with three columns named patient_id, minute and pdr.
- A matrix that can be converted to one of the above.
- A list of data frames/tibbles that are concatenated. When the list has named elements, the names are converted to group labels. When the list elements are not named, group name A is used for all items.
- A structure of class breathtest_data, as imported from a file with read_any_breathtest
- A list of class breathtest_data_list as generated from read function such as read_breathid_xml

.. optional.

use_filename_as_patient_id Always use filename instead of patient name. Use this when patient id are not unique.

Value

A tibble with 4 columns. Column patient_id is created with a dummy entry of pat_a if no patient_id was present in the input data set. A column group is required in the input data if the patients are from different treatment groups or within-subject repeats, e.g. in crossover design. A dummy group name "A" is added if no group column was available in the input data set. If group is present, this is a hint to the analysis functions to do post-hoc breakdown or use it as a grouping variable in population-based methods. A patient can have records in multiple groups, for example in a cross-over designs.

Columns minute and pdr are the same as given on input, but negative minute values are removed, and an entry at 0 minutes is shifted to 0.01 minutes because most fit methods cannot handle the singularity at t=0.

An error is raised if dummy columns patient_id and group cannot be added in a unique way, i.e. when multiple values for a given minute cannot be disambiguated.

Comments are persistent; multiple comments are concatenated with newline separators.

```
options(digits = 4)
# Full manual
minute = seq(0,30, by = 10)
data1 = data.frame(minute,
    pdr = exp_beta(minute, dose = 100, m = 30, k = 0.01, beta = 2))
# Two columns with data at t = 0
data1
# Four columns with data at t = 0.01
cleanup_data(data1)
# Results from simulate_breathtest_data can be passed directly to cleanup_data cleanup_data(simulate_breathtest_data(3))
# .. which implicitly does
```

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```
cleanup_data(simulate_breathtest_data(3)$data)
# Use simulated data
data2 = list(
  Z = simulate_breathtest_data(seed = 10)$data,
  Y = simulate_breathtest_data(seed = 11)$data)
d = cleanup_data(data2)
str(d)
unique(d$patient_id)
unique(d$group)
# "Z" "Y"
# Mix multiple input formats
f1 = btcore_file("350_20043_0_GER.txt")
f2 = btcore_file("IrisMulti.TXT")
f3 = btcore_file("IrisCSV.TXT")
# With a named list, the name is used as a group parameter
data = list(A = read_breathid(f1), B = read_iris(f2), C = read_iris_csv(f3))
d = cleanup_data(data)
str(d)
unique(d$patient_id)
# "350_20043_0_GER" "1871960"
                                      "123456"
# File name is used as patient name if none is available
unique(d$group)
# "A" "B" "C"
```

coef.breathtestfit

S3 coef and summary for breathtestfit

Description

Function coef extracts the estimates such as t50, tlag, from fitted 13C beta exponential models. The result is the same as fit\$coef, but without column stat, which always is "estimate" for nls_fit and nlme_fit.

The summary method only extracts t50 by the Maes/Ghoos method

Usage

```
## S3 method for class 'breathtestfit'
coef(object, ...)
```

Arguments

```
object of class breathtestfit, as returned by nls_fit or nlme_fit
... other parameters passed to methods
```

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Examples

```
# Generate simulated data
data = cleanup_data(simulate_breathtest_data())
# Fit with the population method
fit = nlme_fit(data)
# All coefficients in the long form
coef(fit)
# Access coefficients directly
fit$coef
# Only t50 by Maes/Ghoos
# Can also be used with stan fit (slow!)
## Not run:
if (require("breathteststan")) {
  fit = stan_fit(data, iter = 300, chain = 1)
  coef(fit)
  # We get quantiles here in key/value format
  unique(fit$coef$stat)
}
## End(Not run)
```

coef_by_group

Tabulates per-group breath test parameters

Description

Given a fit to 13C breath test curves, computes absolute values and their confidence intervals of parameters, e.g. of the half emptying time t50. Generic S3 method for class breathtestfit.

Usage

```
coef_by_group(fit, ...)
```

Arguments

```
fit Object of class breathtestfit, for example from nlme_fit, nls_fit or stan_fit
... Not used
```

Value

A tibble of class coef_by_group with columns

```
parameter Parameter of fit, e.g. beta, k, m, t50
```

method Method used to compute parameter. exp_beta refers to primary fit parameters beta,k,m. maes_ghoos uses the method from Maes B D, Ghoos Y F, Rutgeerts P J, Hiele M I, Geypens B and Vantrappen G 1994 Dig. Dis. Sci. 39 S104-6. bluck_coward is the self-correcting method from Bluck L J C and Coward W A 2006

group Grouping parameter of the fit, e.g. patient, normal, liquid, solid

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estimate Parameter estimate

conf.low, conf.high Lower and upper 95 estimate.

diff_group Letters a, b, c indicate that parameter would be in mutually significantly different groups. Letter combinations like ab or abc indicated that this parameter is not significantly different from the given other groups in a Tukey-corrected pairwise test.

Examples

```
library(dplyr)
data("usz_13c")
data = usz_13c %>%
    dplyr::filter( patient_id %in%
        c("norm_001", "norm_002", "norm_003", "norm_004", "pat_001", "pat_002", "pat_003")) %>%
    cleanup_data()
fit = nls_fit(data)
coef_by_group(fit)

fit = nlme_fit(data)
coef_by_group(fit)
```

coef_diff_by_group

Tabulates breath test parameter differences of groups

Description

Given a fit to 13C breath test curves, computes between-group confidence intervals and p-values, for examples of the half emptying time t50, with correction for multiple testing.

Usage

```
coef_diff_by_group(fit, mcp_group = "Tukey", reference_group = NULL, ...)
```

Arguments

fit	Object of class breathtestfit, for example from nlme_fit, nls_fit			
mcp_group	"Tukey" (default) for all pairwise comparisons, "Dunnett" for comparisons reative to the reference group.			
reference_group				
	Used as the first group and as reference group for mcp_group == "Dunnett"			
	Not used			

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Value

A tibble of class coef_diff_by_group with columns

parameter Parameter of fit, e.g. beta, k, m, t50

method Method used to compute parameter. exp_beta refers to primary fit parameters beta,k,m. maes_ghoos uses the method from Maes B D, Ghoos Y F, Rutgeerts P J, Hiele M I, Geypens B and Vantrappen G 1994 Dig. Dis. Sci. 39 S104-6. bluck_coward is the self-correcting method from Bluck L J C and Coward W A 2006

groups Which pairwise difference, e.g solid -liquid

estimate Estimate of the difference

conf.low, conf.high Lower and upper 95 A comparison is significantly different from zero when both estimates have the same sign.

p.value p-value of the difference against 0, corrected for multiple testing

Examples

```
library(dplyr)
data("usz_13c")
data = usz_13c %>%
    dplyr::filter( patient_id %in%
        c("norm_001", "norm_002", "norm_003", "norm_004", "pat_001", "pat_002","pat_003")) %>%
    cleanup_data()
fit = nls_fit(data)
coef_diff_by_group(fit)

# TODO: Add example for Stan fit typecast to class \code{breathtestfit} to compute
# confidence intervals instead of credible intervals
```

cum_exp_beta

Cumulative exponential beta function

Description

Equation (2), page 4 from Bluck, "Recent advances in the interpretation of the 13C octanoate breath test for gastric emptying"

Usage

```
cum_exp_beta(minute, dose, cf)
```

Arguments

minute time in minutes

dose in mg

cf named vector of coefficients; only k and beta are required. Note that k is mea-

sured in 1/min (e_g_ 0_01/min), while often it is quoted as 1/h (e_g_ 0_6/h).

dob_to_pdr

Value

Vector of predicted cumulative pdr

See Also

```
exp_beta
```

dob_to_pdr

Convert breath test DOB data to PDR data

Description

Convert DOB (delta-over-baseline) to PDR for 13C breath test. This is equation (4) in Sanaka, Yamamoto, Tsutsumi, Abe, Kuyama (2005) Wagner-Nelson method for analysing the atypical double-peaked excretion curve in the [13c]-octanoate gastric emptying breath test in humans. Clinical and experimental pharmacology and physiology 32, 590-594.

Usage

```
dob_to_pdr(
  dob,
  weight = 75,
  height = 180,
  mw = 167,
  purity_percent = 99.1,
  mg_substrate = 100
)
```

Arguments

dob Delta-over-baseline vector in 0/00

weight Body weight in kg; assumed 75 kg if missing height Body height in cm; assume 180 cm if missing

mw Molecular weight, 83.023388 g/mol for acetate, 167 g/mol for octanoate. Can

also be given as string "acetate" or "octanoate".

purity_percent Purity in percent mg_substrate Substrate in mg

Value

PDR percent dose/h

Note

I have no idea where the factor 10 in equation (4) comes from, possibly from percent(PDR)/and DOB(0/00). In Kim and Camillieri, Stable isotope breath test and gastric emptying, page 207, a factor of 0.1123 instead of 0.01123 is used, without the factor 10. Which one is correct?

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Examples

```
filename = btcore_file("350_20049_0_GERWithWeight.txt")
bid = read_breathid(filename)
bid$data$pdr1 = dob_to_pdr(bid$data$dob, weight=bid$weight, height=bid$height)

plot(bid$data$minute, bid$data$pdr1, main="points: from breath_id; line: computed", type="1")
points(bid$data$minute, bid$data$pdr,col="red",type="p",pch=16)
#
# Check how far our computed pdr is from the stored pdr
var(bid$data$pdr1-bid$data$pdr)
```

exp_beta

Exponential beta function for 13C breath data

Description

Function to fit PDR time series data to exponential-beta function as given in:

Maes, B. D., B. J. Geypens, Y. F. Ghoos, M. I. Hiele, and P. J. Rutgeerts. 1998. 13C-Octanoic Acid Breath Test for Gastric Emptying Rate of Solids. Gastroenterology 114(4): 856-50

Sanaka M, Nakada K (2010) Stable isotope breath test for assessing gastric emptying: A comprehensive review. J. Smooth Muscle Research 46(6): 267-280

Bluck L J C and Coward W A 2006 Measurement of gastric emptying by the C-13-octanoate breath test — rationalization with scintigraphy Physiol. Meas. 27 279?89

For a review, see

Bluck LJC (2009) Recent advances in the interpretation of the 13C octanoate breath test for gastric emptying. Journal of Breath Research, 3 1-8

Usage

```
exp_beta(minute, dose, m, k, beta)
```

Arguments

minute vector of time values in minutes
dose in mg
m efficiency
k time constant
beta form factor

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Details

```
The function is defined as

exp_beta = function(minute,dose,m,k,beta) {
    m*dose*k*beta*(1-exp(-k*minute))^(beta-1)*exp(-k*minute)}
}
```

At minute == 0, the function behaves like a polynomial with degree (beta-1).

Value

Values and gradients of estimated PDR for use with nls and nlme

See Also

In the example below, data and fit are plotted with standard R graphics. The S3 method plot.breathtestfit provides ggplot2 graphics.

```
start = list(m=20,k=1/100,beta=2)
# fit to real data set and show different t50 results
sample_file = btcore_file("350_20043_0_GER.txt")
# minute 0 must be removed to avoid singularity
breath_id = read_breathid(sample_file)
data = subset(breath_id$data, minute >0)
sample_nls = nls(pdr~exp_beta(minute, 100, m, k, beta), data = data, start = start)
data$pdr_fit_bluck=predict(sample_nls)
plot(data$minute, data$pdr, pch=16, cex=0.7, xlab="time (min)", ylab="PDR",
  main="t50 with different methods")
lines(data$minute,data$pdr_fit_bluck, col="blue")
t50 = t50_bluck_coward(coef(sample_nls))
t50_maes_ghoos = t50_maes_ghoos(coef(sample_nls))
t50scint = t50_maes_ghoos_scintigraphy(coef(sample_nls))
abline(v = t50, col = "red")
abline(v = t50_{maes\_ghoos}, col = "darkgreen", lty = 2)
abline(v = breath_id$t50, col = "black", lty = 4)
abline(v = t50scint, col = "gray", lty = 3)
text(t50, 0, "Self-corrected Bluck/Coward", col = "red", adj = -0.01)
text(breath_id$t50, 0.5, "From BreathID device", col = "black", adj=-0.01)
text(t50scint, 1, " Maes/Ghoos scintigraphic", col = "gray", adj = -0.01)
text(t50_maes_ghoos,1.5, "Classic Maes/Ghoos", col = "darkgreen", adj = -0.01)
# simulated data set
dose = 100
set.seed(4711)
# do not use minute 0, this gives singular gradients
# if required, shift minute = 0 by a small positive amount, e.g. 0.1
# create simulated data
pdr = data.frame(minute=seq(2, 200, by = 10))
```

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```
pdrpdr =
  exp_beta(pdr$minute, 100, start$m, start$k, start$beta) + rnorm(nrow(pdr), 0, 1)
par(mfrow = c(1, 2))
# plot raw data
plot(pdr$minute, pdr$pdr, pch=16, cex=0.5, xlab = "time (min)",ylab = "PDR")
# compute fit
pdr_nls = nls(pdr~exp_beta(minute, 100, m, k, beta), data = pdr, start = start)
# compute prediction
pdr$pd_rfit = predict(pdr_nls)
lines(pdr$minute, pdr$pd_rfit, col="red", lwd=2)
# plot cumulative
plot(pdr$minute, cum_exp_beta(pdr$minute,100,coef(pdr_nls)), type="l",
     xlab = "time (min)", ylab = "cumulative PDR")
# show t50
t50 = t50_bluck_coward(coef(pdr_nls))
tlag = tlag_bluck_coward(coef(pdr_nls))
abline(v = t50, col = "gray")
abline(v = tlag,col = "green")
abline(h = 50, col = "gray")
# create simulated data from several patients
pdr1 = data.frame(patient = as.factor(letters[1:10]))
pdr1$m = start$m*(1 + rnorm(nrow(pdr1), 0, 0.1))
pdr1$k = start$k*(1 + rnorm(nrow(pdr1), 0, 0.3))
pdr1$beta = start$beta*(1 + rnorm(nrow(pdr1), 0, 0.1))
pdr1 = merge(pdr1, expand.grid(minute = seq(2, 200, by = 10),
   patient = letters[1:10]))
pdr1 = pdr1[order(pdr1$patient, pdr1$minute), ]
# simulated case: for patient a, only data up to 50 minutes are available
pdr1 = pdr1[!(pdr1$patient == "a" & pdr1$minute > 50),]
set.seed(4711)
pdr1pdr =
  with(pdr1, exp_beta(minute, 100, m, k, beta) + rnorm(nrow(pdr1), 0, 1))
# compute nls fit for patient a only: fails
# the following line will produce an error message
pdr_nls = try(nls(pdr~exp_beta(minute, 100, m, k, beta), data=pdr1, start=start,
                  subset = patient=="a"))
stopifnot(class(pdr_nls) == "try-error")
# use nlme to fit the whole set with one truncated record
suppressPackageStartupMessages(library(nlme))
pdr_nlme = nlme(pdr~exp_beta(minute,100,m,k,beta), data = pdr1,
                fixed = m+k+beta^1,
                random = m+k+beta^1,
                groups = ~patient,
                start = c(m = 20, k = 1/100, beta = 2))
coef(pdr_nlme)
pred_data = expand.grid(minute = seq(0, 400, 10), patient = letters[1:10])
```

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extract_id

Extracts an ID from string IRIS CSV file

Description

First tries to extract only digits, separating these by underscore when there are multiple blocks. If this give a non-valid id, returns the whole string without spaces and periods, hoping it makes sense. For internal use, but should be overridden for exotic IDs

Usage

```
extract_id(id)
```

Arguments

id

One item from column Identifikation, e.g. "KEK-ZH-Nr.2013-1234"

Examples

extract_id

nlme_fit

Mixed-model nlme fit to 13C Breath Data

Description

Fits exponential beta curves to 13C breath test series data using a mixed-model population approach. See https://menne-biomed.de/blog/breath-test-stan for a comparison between single curve, mixed-model population and Bayesian methods.

Usage

```
nlme_fit(
  data,
  dose = 100,
  start = list(m = 30, k = 1/100, beta = 2),
  sample_minutes = 15
)
```

nlme_fit

Arguments

data Data frame or tibble as created by cleanup_data, with mandatory columns patient_id,group,minute and pdr. It is recommended to run all data through cleanup_data to insert dummy columns for patient_id and group if the data are distinct, and report an error if not. At least 2 records are required for a population fit, but 10 or more are recommended to obtain a stable result. Dose of acetate or octanoate. Currently, only one common dose for all records dose is supported. The dose only affects parameter m of the fit; all important t50parameters are unaffected by the dose. start Optional start values. In most case, the default values are good enough to achieve convergence, but slightly different values for beta (between 1 and 2.5) can save a non-convergent run. sample_minutes When the mean sampling interval is < sampleMinutes, data are subsampled using a spline algorithm by function subsample_data. See the graphical output of plot.breathtestfit for an example where too densely sampled data of one patients were subsampled for the fit.

Value

A list of class ("breathtestnlmefit" "breathtestfit") with elements

coef Estimated parameters in a key-value format with columns patient_id, group, parameter, stat, method and value. Parameter stat currently always has value "estimate". Confidence intervals will be added later, so do not take for granted that all parameters are estimates. Has an attribute AIC which can be retrieved by the S3-function AIC.

data The data effectively fitted. If points are to closely sampled in the input, e.g. with BreathId devices, data are subsampled before fitting.

See Also

Base methods coef, plot, print; methods from package broom: tidy, augment.

```
d = simulate_breathtest_data(n_records = 3, noise = 0.7, seed = 4712)
data = cleanup_data(d$data)
fit = nlme_fit(data)
plot(fit) # calls plot.breathtestfit
options(digits = 3)
library(dplyr)
cf = coef(fit)
# The coefficients are in long key-value format
cf
# AIC can be extracted
AIC(fit)
# Reformat the coefficients to wide format and compare
# with the expected coefficients from the simulation
# in d$record.
cf %>%
```

nls_fit

nls_fit

Individual curve fit with nls to 13C breath test data

Description

Fits individual exponential beta curves to 13C breath test time series

Usage

```
nls_fit(data, dose = 100, start = list(m = 50, k = 1/100, beta = 2))
```

Arguments

data	Data frame or tibble as created by cleanup_data, with mandatory columns patient_id,group,minute and pdr. It is recommended to run all data through cleanup_data which will insert dummy columns for patient_id and minute if the data are distinct, and report an error if not.
dose	Dose of acetate or octanoate. Currently, only one common dose for all records is supported.
start	Optional start values patient_id and group.

Value

A list of class ("breathtestnlsfit" "breathtestfit") with elements

coef Estimated parameters in a key-value format with columns patient_id, group, parameter, stat, method and value. Parameter stat always has value "estimate". Confidence intervals might be added later, so do not take for granted all parameters are estimates.

data Input data; nls_fit does not decimate the data. If you have large data sets where subsampling might be required to achieve faster convergence, using nls_fit anyway is only relevant to show how NOT to do it. Use nlme_fit or stan_fit instead.

See Also

Base methods coef, plot, print; methods from package broom: tidy, augment.

20 null_fit

Examples

null_fit

Convert data to class breathtestfit

Description

Does not change the data set, but returns a class suitable for plotting raw data with plot.breathtestfit. See read_any_breathtest for an example.

Usage

```
null_fit(data, ...)
```

Arguments

Data frame or tibble as created by cleanup_data, with mandatory columns patient_id,group,minute and pdr.

... Not used

Value

A list of classes breathtestnullfit, breathtestfit with element data which contains the unmodified data.

plot.breathtestfit 21

plot.breathtestfit S3 plot method for breathtestfit

Description

Plots 13C data and fits.

Usage

```
## S3 method for class 'breathtestfit'
plot(
    x,
    inc = 5,
    method_t50 = "maes_ghoos",
    line_size = 1,
    point_size = NULL,
    ...
)
```

Arguments

```
x object of class breathtestfit, as returned by nls_fit, nlme_fit, null_fit
    or stan_fit; stan_fit is in package breathteststan,
inc Increment for fitted curve plot in minutes

method_t50 Method for t50: "maes_ghoos", "bluck_coward" or "maes_ghoos_scintigraphy"
line_size optional line width; can improve look for printouts
point_size optional point size; determined dynamically when NULL
    other parameters passed to methods. Not used
```

```
data = list(
   A = simulate_breathtest_data(n_records = 6, seed = 100),
   B = simulate_breathtest_data(n_records = 4, seed = 187)
)
# cleanup_data combines the list into a data frame
x = nls_fit(cleanup_data(data))
plot(x)
```

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read_any_breathtest

Read breathtest files of any format

Description

Uses breathtest_read_function to determine the file type and reads it if it has a valid format.

Usage

```
read_any_breathtest(files)
```

Arguments

files

A single filename, a list or a character vector of filenames.

Value

A list of breathtest_data, even if only one file was passed. The list can be passed to cleanup_data to extract one concatenated data frame for processing with nls_fit, nlme_fit, null_fit (no processing) or stan_fit in separate package breathteststan.

Examples

```
files = c(
  group_a = btcore_file("IrisCSV.TXT"),
  group_a = btcore_file("350_20043_0_GER.txt"),
  group_b = btcore_file("IrisMulti.TXT"),
  group_b = btcore_file("NewBreathID_01.xml")
)
bt = read_any_breathtest(files)
str(bt, 1)
# Passing through cleanup_data gives a data frame/tibble
bt_df = cleanup_data(bt)
str(bt_df)
# If you want data only, use null_fit()
plot(null_fit(bt_df))
# Plot population fit with decimated data
plot(nlme_fit(bt_df))
```

read_breathid

Read BreathID file

Description

Reads 13c data from a BreathID file, and returns a structure of class breathtest_data.

read_breathid_xml 23

Usage

```
read_breathid(filename = NULL, text = NULL)
```

Arguments

filename name of txt-file to be read

text alternatively, text can be given as string

Value

Structure of class breathtest_data

Examples

```
filename = btcore_file("350_20043_0_GER.txt")
# Show first lines
cat(readLines(filename, n = 10), sep="\n")
#
bid = read_breathid(filename)
str(bid)
```

read_breathid_xml

Read new BreathID/Examens XML file

Description

Reads 13c data from an XML BreathID file, and returns a structure of class breathtest_data_list, which is a list with elements of class breathtest_data.

Usage

```
read_breathid_xml(filename = NULL, text = NULL)
```

Arguments

filename name of xml-file to be read

text alternatively, text can be given as string

Value

List of class breathtest_data_list of structures of class breathtest_data; an XML file can contain multiple data sets.

Examples

```
filename = btcore_file("NewBreathID_01.xml")
# Show first lines
cat(readLines(filename, n = 10), sep="\n")
bid = read_breathid_xml(filename)
# List with length 1
str(bid, 1)
filename = btcore_file("NewBreathID_multiple.xml")
bids = read_breathid_xml(filename)
str(bids, 1) # 3 elements - the others in the file have no data
# Create hook function to deselect first record
choose_record = function(records) {
 r = rep(TRUE, length(records))
 r[1] = FALSE
}
options(breathtestcore.choose_record = choose_record)
bids = read_breathid_xml(filename)
str(bids, 1) # 2 elements, first deselected
```

read_breathtest_excel Reads breathtest data in Excel format

Description

Can read several formats of data sets in Excel, from 2 (minute,pdr or dob for 1 record) to 4 columns (patient_id,group,minute,pdr or dob). Conversion from dob to pdf is done for assuming 180 cm height and 75 kg weight. See the example below with several sheets for supported formats

Usage

```
read_breathtest_excel(filename, sheet = 1)
```

Arguments

filename Name of Excel-file to be read

sheet Name or number of Excel file to be read. When used with read_any_breathtest,

the first sheet is always read. You must call read_breathtest_excel explicitly

to read other worksheets, as shown in the example below.

Value

Different from the other readXXX function, this returns a list with a data frame, not a structure of breathtest_data. Pass result through cleanup_data to make it compatible with other formats.

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Examples

```
filename = btcore_file("ExcelSamples.xlsx")
sheets = readxl::excel_sheets(filename)
# First 4 lines of each sheet
for (sheet in sheets) {
   cat("\nSheet ", sheet,"\n")
   ex = readxl::read_excel(filename, sheet = sheet, n_max = 4)
   print(ex)
}
# To get consistently formatted data from a sheet
bt_data = read_breathtest_excel(filename, sheets[6])
# 3 columns
str(bt_data)
bt_cleaned = cleanup_data(bt_data)
# 4 columns standard format
str(bt_cleaned)
```

read_iris

Read 13C data from IRIS/Wagner Analysen

Description

Reads composite files with 13C data from IRIS/Wagner Analysen. The composite files start as follows:

```
"Testergebnis"
"Nummer","1330"
"Datum","10.10.2013"
"Testart"
```

Usage

```
read_iris(filename = NULL, text = NULL)
```

Arguments

filename name of IRIS/Wagner file in composite format text alternatively, text can be given as string

Value

List of class breathtest_data with file_name, patient_name, patient_first_name, test, identifikation, and data frame data with time and dob

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Examples

```
filename = btcore_file("IrisMulti.TXT")
cat(readLines(filename, n = 10), sep="\n")
#
iris_data = read_iris(filename)
str(iris_data)
```

read_iris_csv

Read 13C data from IRIS/Wagner Analysen in CSV Format

Description

Reads 13C data from IRIS/Wagner Analysen in CSV Format The CSV files start as follows:

```
"Name", "Vorname", "Test", "Identifikation"
```

This format does not have information about the substrate (acetate, octanoate), the dose and body weight and height. The following defaults are used: substrate = acetate, dose = 100, weight = 75, height = 180.

Usage

```
read_iris_csv(filename = NULL, text = NULL)
```

Arguments

filename Name of IRIS/Wagner file in CSV format text alternatively, text can be given as string

Value

List of class breath_test_data with file name, patient name, patient first name, test, identifikation, and data frame data with time and dob

```
filename = btcore_file("IrisCSV.TXT")
cat(readLines(filename, n = 3), sep="\n")
#
iris_data = read_iris_csv(filename)
str(iris_data)
```

sigma.breathtestnlmefit 27

```
sigma.breathtestnlmefit
```

S3 method to extract the fit's residual standard deviation

Description

Functions for nls and nlme are available; additional functions for Stan-based fits are defined in package breathteststan.

Usage

```
## S3 method for class 'breathtestnlmefit'
sigma(object, ...)
```

Arguments

```
object Result of class breathtestfit ... Not used
```

Value

A numeric value giving the standard deviation of the residuals.

```
simulate_breathtest_data
```

Simulate 13C breath time series data

Description

Generates simulated breath test data, optionally with errors. If none of the three standard deviations m_std,k_std,beta_std is given, an empirical covariance matrix from USZ breath test data is used. If any of the standard deviations is given, default values for the others will be used.

Usage

```
simulate_breathtest_data(
    n_records = 10,
    m_mean = 40,
    m_std = NULL,
    k_mean = 0.01,
    k_std = NULL,
    beta_mean = 2,
    beta_std = NULL,
    noise = 1,
    cov = NULL,
```

```
student_t_df = NULL,
missing = 0,
seed = NULL,
dose = 100,
first_minute = 5,
step_minute = 15,
max_minute = 155
)
```

Arguments

n_records	Number of records			
m_mean, m_std	Mean and between-record standard deviation of parameter m giving metabolized fraction.			
k_mean, k_std	Mean and between-record standard deviation of parameter k, in units of 1/minutes.			
beta_mean, beta_std				
	Mean and between-record standard deviations of lag parameter beta			
noise	Standard deviation of normal noise when student_t_df = NULL; scaling of noise when student_t_df $>= 2$.			
cov	Covariance matrix, default NULL, i.e. not used. If given, overrides standard deviation settings.			
student_t_df	When NULL (default), Gaussian noise is added; when >= 2, Student_t distributed noise is added, which generates more realistic outliers. Values from 2 to 5 are useful, when higher values are used the result comes close to that of Gaussian noise. Values below 2 are truncated to 2.			
missing	When 0 (default), all curves have the same number of data points. When > 0 , this is the fraction of points that were removed randomly to simulate missing			
seed	Optional seed; not set if seed = NULL (default)			
dose	Octanoate/acetate dose, almost always 100 mg, which is also the default			
first_minute	First sampling time. Do not use 0 here, some algorithms do not converge when data near 0 are passed.			
step_minute	Inter-sample interval for breath test			
max_minute	Maximal time in minutes.			

Value

A list of class simulated_breathtest_data with 2 elements:

record Data frame with columns patient_id(chr), m, k, beta, t50 giving the effective parameters for the individual patient record.

data Data frame with columns patient_id(chr),minute(dbl),pdr(dbl) giving the time series and grouping parameters.

A comment is attached to the return value that can be used as a title for plotting.

subsample_data 29

Examples

subsample_data

Decimate densely sampled 13C time series

Description

When data of a record are more closely spaced than sample_minutes, these are spline-subsampled to sample_minutes. In the region of the initial slope, i.e. the initial fifth of the time, the record is sampled more densely. Too dense sampling leads to non-convergent nlme fits and to long runs with Stan-based fits. The function is used internally by function link{nlme_fit} in package breathtestcore and is exported for use by package breathteststan.

Usage

```
subsample_data(data, sample_minutes)
```

Arguments

data Data frame with columns patient_id,group,minute,pdr.
sample_minutes Required average density. When points are more closely spaced, data are subsampled. No upsampling occurs when data are more sparse.

t50_bluck_coward

Bluck-Coward self-corrected half-emptying time

Description

Uses Newton's method to solve the self-corrected Bluck-Coward equation for 1/2 to compute the half-emptying time t_50.

See also equation G(n,t) in

Bluck LJC, Jackson S, Vlasakakis G, Mander A (2011) Bayesian hierarchical methods to interpret the 13C-octanoic acid breath test for gastric emptying. Digestion 83_96-107, page 98.

30 t50_bluck_coward

Usage

```
t50_bluck_coward(cf)
```

Arguments

cf

Named vector of coefficients; only k and beta are required. In this package, k is measured in units of 1/min (e.g. 0.01/min), in publications it is often quoted as 1/h (e.g. 0.6/h).

Value

Time where value is 1/2 of the maximum, i.e. t_50 or $t_1/2$ in minutes; in the publication by Bluck et al, the parameter is called $t_1/2$ (in).

See Also

```
exp_beta
```

```
# From table 3 and 4 in Bluck et al.; values for \code{k} and \code{beta}
# (nls, bayesian) are entered and checked against the tabulated values of
# t_{1/2(in)}.
# Most errors are small, but there are some outliers; errors in paper table?
# Parameters and Bluck et al. results:
# table 3 of Bluck et al.
cf3 = data.frame(
          method = rep(c("nls", "bayesian")),
          group = rep(c("lean", "obese"),each=2),
          k =
                 c(0.576, 0.606, 0.529, 0.608),
          beta = c(5.24, 5.79, 5.95, 7.54),
          t12 = c(3.67, 3.63, 4.23, 3.99),
          t12in = c(2.076, 2.110, 2.422, 2.466),
          tlag = c(2.88, 2.88, 3.34, 3.26),
          tlagin = c(1.632, 1.724, 1.92, 2.101)
cf3 = dplyr::mutate(cf3,
          t50_maes_ghoos = t50_maes_ghoos(cf3),
          t50_bluck_coward = t50_bluck_coward(cf3),
          tlag_maes_ghoos = tlag_maes_ghoos(cf3),
          tlag_bluck_coward = tlag_bluck_coward(cf3),
          err_t50_maes_ghoos = round(100*(t50_maes_ghoos-t12)/t12, 2),
          err_t50_bluck_coward =
            round(100*(t50_bluck_coward-t12in)/t12in, 2),
          err_lag_maes = round(100*(tlag_maes_ghoos-tlag)/tlag,2),
          err_lag_bluck_coward =
            round(100*(tlag_bluck_coward-tlagin)/tlagin,2)
)
cf3
# table 4
# there are large differences for mj3, both using the bayesian (26%)
```

t50_maes_ghoos 31

```
# and the nls method (16%). The other data are within the expected limits
cf4 = data.frame(
         method = rep(c("nls", "bayesian"),each=3),
          group = rep(c("mj1",
                                "mj2",
                                          "mj3")),
         k = c(0.585, 0.437, 0.380, 0.588, 0.418, 0.361),
         beta=c(4.35, 4.08, 4.44, 4.49, 4.30, 4.29),
          t12 = c(3.39, 4.25, 4.82, 3.40, 4.61, 5.09),
          t12in = c(1.77, 2.16, 2.19, 1.81, 2.34, 2.43),
          tlag = c(2.56, 3.17, 3.39, 2.58, 3.40, 3.62),
          tlagin = c(1.30, 1.53, 1.33, 1.35, 1.65, 1.57)
cf4 = dplyr::mutate(cf4,
          t50_maes_ghoos = t50_maes_ghoos(cf4),
          t50_bluck_coward = t50_bluck_coward(cf4),
          tlag_maes_ghoos = tlag_maes_ghoos(cf4),
          tlag_bluck_coward = tlag_bluck_coward(cf4),
          err_t50_maes_ghoos = unlist(round(100*(t50_maes_ghoos-t12)/t12)),
          err_t50_bluck_coward =
           round(100*(t50_bluck_coward-t12in)/t12in,2),
          err_lag_maes = round(100*(tlag_maes_ghoos-tlag)/tlag,2),
          err_lag_bluck_coward =
           round(100*(tlag_bluck_coward-tlagin)/tlagin,2)
)
cf4
```

t50_maes_ghoos

Half-emptying time by Maes/Ghoos method

Description

Half-emptying time t50 as determined from the fit of a beta exponential function. In the Maes/Ghoos model, it is defined as the time when the area under curve (AUC) is 50% of the AUC from 0 to infinity.

Maes B D, Ghoos Y F, Rutgeerts P J, Hiele M I, Geypens B and Vantrappen G 1994 Dig. Dis. Sci. 39 S104-6.

Usage

```
t50_maes_ghoos(cf)
```

Arguments

cf

named vector of coefficients; only k and beta are required note that k is measured in 1/min (e.g. 0.01/min), usually it is quoted as 1/h (e.g. 0.6/h).

Value

Time in minutes when area under curve is 50% of the AUC to infinity. In the Maes/Ghoos model, this is used as a surrogate for gastric emptying half time t50.

See Also

```
exp_beta, and t50_bluck_coward for an example.
```

Examples

```
# Integral from 0 to infinity is 100 at dose 100 mg integrate(exp_beta, 0, Inf, beta = 1.5, k = 0.01, m = 1, dose = 100) t50_mg = t50_maes_ghoos(c(beta = 1.5, k = 0.01, dose = 100)) t50_mg # Integral to half-emptying time \code{t50_maes_ghoos} is 50 integrate(exp_beta, 0, t50_mg, beta = 1.5, k = 0.01, m = 1, dose = 100)
```

```
t50_maes_ghoos_scintigraphy
```

Half-emptying time t50 from Maes/Ghoos fit with scintigraphic correction

Description

Half-emptying time t50 in minutes from beta exponential function fit, with linear and rather arbitrary correction for scintigraphic values. This is given for comparison with published data only; there is little justification to use it, even if it is closer to real gastric emptying times as determined by MRI or scintigraphy. Ghoos YF, Maes BD, Geypens BJ, Mys G, Hiele MI, Rutgeerts PJ, Vantrappen G. Measurement of gastric emptying rate of solids by means of a carbon-labeled octanoic acid breath test. Gastroenterology. 1993;104:1640-1647.

Usage

```
t50_maes_ghoos_scintigraphy(cf)
```

Arguments

cf

named vector of coefficients; only k and beta are required

Value

Time where value is 1/2 of maximum, i.e. t50 in minutes.

See Also

```
exp_beta, and t50_bluck_coward for an example.
```

tidy.breathtestfit 33

tidy.breathtestfit Broom-style tidying methods for breathtestfit

Description

Broom-method tidy to streamline the results of class breathttestfit as generated by nls_fit or nlme_fit. Returns the fit coefficients and half-emptying time t50 with the Maes/Ghoos method; additional parameters should be extracted with coef.

Usage

```
## S3 method for class 'breathtestfit'
tidy(x, ...)
```

Arguments

x Object of class breathttestfit... other parameters passed to methods

Value

A tibble/data frame with columns

```
patient_id Patient Id (character)
group Treatment or patient group (character)
m Fraction metabolized
k Time constant (1/minutes)
beta The so-called lag parameters, no dimension
t50 Emptying half time in minutes as calculated following Maes/Ghoos
```

See Also

tidy

```
library(broom)
# Generate simulated data
data = cleanup_data(simulate_breathtest_data()$data)
# Fit with the population method
fit = nlme_fit(data)
# Output coefficients
tidy(fit)
# All coefficients in the long form
coef(fit)
```

34 tlag_maes_ghoos

tlag_bluck_coward

Lag phase for Bluck-Coward self-correcting fit

Description

This parameter is probably not very useful, as it can be negative

Usage

```
tlag_bluck_coward(cf)
```

Arguments

cf

named vector of coefficients; only k and beta are required. Note that in this package, k is measured in 1/min (e.g. 0.01/min), while in the literature is is often quoted as 1/h (e.g. 0.6/h).

Value

Lag phase in minutes (time t at which the maximum in the rate of change of g(t) occurs)

See Also

exp_beta, and t50_bluck_coward for an example.

tlag_maes_ghoos

So-called lag time from Maes/Ghoos fit

Description

Computes tlag from uncorrected fit to the beta exponential function. The name tlag is a misnomer; it simply is the maximum of the PDR curve, so in papers by Bluck et al. it is renamed to t_max.

Maes B D, Ghoos Y F, Rutgeerts P J, Hiele M I, Geypens B and Vantrappen G 1994 Dig. Dis. Sci. 39 S104-6.

Usage

```
tlag_maes_ghoos(cf)
```

Arguments

cf

named vector of coefficients; only k and beta are required k is measured in $1/\min$ (e.g. $0.01/\min$).

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Value

Lag time as defined from Maes/Ghoos fit

See Also

exp_beta, and t50_bluck_coward for an example.

usz_13c

Zurich sample set of 13C breath test data

Description

13C time series PDR data from normals and random patients from the division of Gastroenterology and Hepatology, University Hospital Zurich. Most breath samples from normals were collected with bags and analyzed by IRIS/Wagner infrared spectroscopy. Patient samples were recorded with the continuous monitoring system BreathID.

patient_id Patient identifier, starting with norm for normals (healthy volunteers) and pat for patients. Note that for normals there are two records for each subject, so only the combination of patient_id and group is a unique identifier of the time series record.

group liquid_normal for normals and liquid meal, solid_normal normals and solid meal, and patient for patients from the University Hospital of Zurich.

minute Time in minutes

pdr PDR as computed by breathtest device or from dob via function dob_to_pdr

Usage

```
data(usz_13c)
```

Format

A data frame with 15574 rows and 4 variables

```
data(usz_13c)
## Not run:
str(usz_13c)
# Plot all records; this needs some time
pdf(file.path(tempdir(), "usz_13c.pdf"), height= 30)
# null_fit makes data plotable without fitting a model
plot(null_fit(usz_13c))
dev.off()

## End(Not run)
# Plot a subset
suppressPackageStartupMessages(library(dplyr))
```

36 usz_13c_d

```
usz_part = usz_13c %>%
filter(patient_id %in% c("norm_001","norm_002", "pat_001", "pat_002"))
plot(null_fit(usz_part))
```

usz_13c_a

Exotic 13C breath test data

Description

13C time series PDR data from three different groups in a randomized (= not-crossover) design. This are unpublished data from Gastroenterology and Hepatology, University Hospital Zurich.

Data are formatted as described in usz_13c. These time series present a challenge for algorithms.

Usage

```
data(usz_13c_a)
```

Examples

```
library(dplyr)
library(ggplot2)
data(usz_13c_a)
d = usz_13c_a %>%
    cleanup_data() %>% # recommended to test for validity
    nlme_fit()
plot(d)
```

usz_13c_d

13C breath test data with MRI emptying for comparison

Description

13C time series PDR data from normals and three different meals in a cross-over design from the division of Gastroenterology and Hepatology, University Hospital Zurich. See Kuyumcu et al., Gastric secretion does not affect....

Data are formatted as described in usz_13c. In addition, half emptying times from MRI measurements are attached to the data as attribute mri_t50. The example below shows how to analyze the data and present half emptying times from MRI and 13C in diagrams.

Usage

```
data(usz_13c_d)
```

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```
library(dplyr)
library(ggplot2)
data(usz_13c_d)
mri_t50 = attr(usz_13c_d, "mri_t50")
d = usz_13c_d \%
  cleanup_data() %>% # recommended to test for validity
  nlme_fit()
plot(d) +
  geom_vline(data = mri_t50, aes(xintercept = t50), linetype = 2)
# Maes-Ghoos t50
dd = mri_t50 %>%
 inner_join(
   coef(d) %>% filter(parameter=="t50", method == "maes_ghoos"),
   by = c("patient_id", "group")) %>%
 mutate(
    t50_{maes\_ghoos} = value
 )
ggplot(dd, aes(x=t50, y = t50_maes_ghoos, color = group)) +
  geom_point() +
  facet_wrap(~group) +
  geom_abline(slope = 1, intercept = 0) +
  xlim(45,205) +
  ylim(45,205)
# Bluck-Coward t50
dd = mri_t50 %>%
  inner_join(
    coef(d) %>% filter(parameter=="t50", method == "bluck_coward"),
   by = c("patient_id", "group")) %>%
  mutate(
    t50_bluck_coward = value
ggplot(dd, aes(x=t50, y = t50_bluck_coward, color = group)) +
  geom_point() +
  facet_wrap(~group) +
  geom_abline(slope = 1, intercept = 0) +
  xlim(0,205) +
  ylim(0,205)
```

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