

Package: loewesadditivity (via r-universe)

September 11, 2024

Title Loewe's Additivity

Version 0.1.0

Description Estimate model parameters to determine whether two compounds have synergy, antagonism, or Loewe's Additivity.

License MIT + file LICENSE

Depends R (>= 3.1.0)

Encoding UTF-8

LazyData true

Suggests testthat (>= 2.1.0), knitr, rmarkdown, kableExtra, devtools

Imports dplyr, tidyr, magrittr, rlang, ggplot2, metR, gridExtra, rootSolve, viridis

RoxygenNote 7.0.2

VignetteBuilder knitr

Repository <https://skgallagher.r-universe.dev>

RemoteUrl <https://github.com/skgallagher/loewesadditivity>

RemoteRef HEAD

RemoteSha 1b62f3e6a468e7214ef684f4fff27bdc7337e3e9

Contents

base_GIA	2
boot_GIA	3
calc_S	4
calc_S_base	5
cyrpa_ripr	5
design_experiment	6
design_grid	7
estimate_GIA	7
estimate_params	8
fortify_gia_data	10
get_ed_line	10

make_grid	11
plot_curves	12
plot_isobologram	13
plot_surface	14
rh5_ama1ron2	16
rh5_rh4	16
simulate_coverage	17
SSE_GIA	18

Index	20
--------------	-----------

base_GIA	<i>Estimate GIA according to the base model</i>
----------	---

Description

Estimate GIA according to the base model

Usage

```
base_GIA(model_params, dose_A, dose_B, fn_list = NULL)
```

Arguments

model_params	named vector of parameters to be used in function. Specifically, the named parameters must be "beta_A", "beta_B", "gamma_A", "gamma_B", "tau_1", and "tau_2". See details for more info.
dose_A	numeric vector of doses (e.g. mg/mL) of dose_A
dose_B	numeric vector of doses (e.g. mg/mL) of dose_B
fn_list	NULL

Value

estimated GIA for each combination of dose A and dose B

Details

The equation is given in full as follows. The GIA (%) is given as a function of the model parameters and the doses A_i and B_i , respectively. The doses scaled by the respective ED50s β_A and β_B are denoted by A_i^* and B_i^* , respectively. The parameters γ_A and γ_B are shape parameters. The parameters τ_1 and τ_2 are interaction parameters. Finally, λ_i is a weighted combination of dose A and dose B.

$$GIA_i = 100\%(1 - e^{-\psi_i})$$

$$\psi_i = \log(2)u_i^{v_i}$$

$$u_i = A_i^* + B_i^* + \tau_1 A_i^* B_i^*$$

$$v_i = \lambda_i \gamma_A + (1 - \lambda_i) \gamma_B + \tau_1 \tau_2 \lambda_i (1 - \lambda_i) \gamma_A \gamma_B$$

$$\lambda_i = \frac{A_i^*}{A_i^* + B_i^*}$$

$$A_i^* = A_i/\beta_A$$

$$B_i^* = B_i/\beta_B$$

Examples

```
model_params <- c("beta_A" = 1, "beta_B" = 2, "gamma_A" = .5,
  "gamma_B" = .6, "tau_1" = 1, "tau_2" = 0)
dose_A <- c(0, 1, 0)
dose_B <- c(0, 0, 1)
base_GIA(model_params, dose_A, dose_B)
```

 boot_GIA

Helper function for the bootstrap results

Description

Helper function for the bootstrap results

Usage

```
boot_GIA(
  par,
  gia_df,
  gia_est,
  n_boot = 100,
  alpha = 0.05,
  GIA_fn = base_GIA,
  S_fn = calc_S_base,
  fn_list = NULL,
  verbose = FALSE
)
```

Arguments

par	named vector of parameters, that correspond to those used in 'GIA_fn'.
gia_df	data frame with the following columns <ul style="list-style-type: none"> • dose_Adose A mg/mL • dose_Bdose B mg/mL • GIAGIA
gia_est	estimated values of GIA (these will be used as the 'truth')
n_boot	number of boot straps to use to estimate confidence intervals of the parameters, GIA estimates, and values of S. The default is 100. If n_boot = 0, then no bootstraps will be run and only the point estimates will be returned.

alpha	value of alpha. Default is .05
GIA_fn	function to calculate the GIA from dose_A and dose_B combinations and given set of parameters. Default is base_GIA
S_fn	Function to calculate S. Default is calc_S_base
fn_list	additional arguments to pass to GIA_fn
verbose	logical indicating whether we should print where we are in the process. Default is FALSE.

Value

a list with the following elements

- params_esta data frame of dimension # of params x 4 where each row in the data frame is a parameter and where the columns are the mean, lower, alpha/2 quantile, and upper, 100 - alpha/2 quantile
- S_est a data frame of one row x 4 where we provide the mean, lower, and upper estimates
- GIA_est the original data with additional columns of the mean, lower, and upper estimates for each dose combination

calc_S	<i>Calculate S generally</i>
--------	------------------------------

Description

Calculate S generally

Usage

```
calc_S(best_pars, S_fn = calc_S_base, fn_list = NULL)
```

Arguments

best_pars	named vector of parameters. "tau_1" must be a name. As must "tau_2" and "gamma_A" and "gamma_B"
S_fn	function to calculate
fn_list	NULL

Value

Hewlett's S for the given model

Examples

```
best_pars <- c("tau_1" = 0,
              "tau_2" = 1,
              "gamma_A" = 1,
              "gamma_B" = 1)
calc_S_base(best_pars) # should be 1
```

calc_S_base	<i>Calculate S from given tau_1 for base model</i>
-------------	--

Description

Calculate S from given tau_1 for base model

Usage

```
calc_S_base(best_pars, fn_list = NULL)
```

Arguments

best_pars	named vector of parameters. "tau_1" must be a name. As must "tau_2" and "gamma_A" and "gamma_B"
fn_list	NULL

Value

Hewlett's S for the base model.

Examples

```
best_pars <- c("tau_1" = 0,
              "tau_2" = 1,
              "gamma_A" = 1,
              "gamma_B" = 1)
calc_S_base(best_pars) # should be 1
```

cyrpa_ripr	<i>CyRPA and RIPR</i>
------------	-----------------------

Description

The data is the raw data for a combination dose of CyRPA and RIPR.

well one of iRBC (the max), uRBC (the min), RPMI (??), or comb (which is short for combination)

RIPR dose of RIPR in mg/mL

CyRPA dose of CyRPA in mg/mL

expyrepxz the results from experiment x, sub item y, repetition z

Usage

```
cyrpa_ripr
```

Format

An object of class `data.frame` with 38 rows and 15 columns.

Examples

```
data("cyrpa_ripr")
head(cyrpa_ripr)
```

design_experiment	<i>Helper function to generate code to run an experiment</i>
-------------------	--

Description

Helper function to generate code to run an experiment

Usage

```
design_experiment(
  levels_A = c(0, 1 * 2^(-4:2)),
  levels_B = c(0, 2 * 2^(-4:2)),
  par = c(beta_A = 1, beta_B = 2, gamma_A = 0.5, gamma_B = 0.5, tau_1 = 3, tau_2 = 0.05),
  n_rep = 1,
  n_sims = 100,
  noise_par = c(a0 = 3, a1 = 0.01)
)
```

Arguments

levels_A	levels of A used in the combination
levels_B	levels of B used in the combination
par	named vector of model parameters
n_rep	number of total repetitions of experiment
n_sims	number of simulations to run
noise_par	named vector with 'a0' and 'a1' which are used to generate noise for the GIA.

Details

prints out code to copy and paste into R to simulate the expected coverage of your experiment under your designed hypothesis

design_grid	<i>Function to design an experimental grid of combinations</i>
-------------	--

Description

Function to design an experimental grid of combinations

Usage

```
design_grid(
  levels_A = c(0, 1 * 2^(-4:2)),
  levels_B = c(0, 2 * 2^(-4:2)),
  n_rep = 1
)
```

Arguments

levels_A	levels of A used in the combination
levels_B	levels of B used in the combination
n_rep	number of total repetitions of experiment

Value

data frame with columns dose_A, dose_B, and GIA for all possible combinations

estimate_GIA	<i>Take in dose A and dose B combinations and estimate GIA</i>
--------------	--

Description

Take in dose A and dose B combinations and estimate GIA

Usage

```
estimate_GIA(model_params, dose_A, dose_B, fn = base_GIA, fn_list = NULL)
```

Arguments

model_params	named vector of parameters to be used in function
dose_A	numeric vector of doses (e.g. mg/mL) of dose_A
dose_B	numeric vector of doses (e.g. mg/mL) of dose_B
fn	the function used to calculate GIA. The default is base_GIA. See ?base_GIA for more details.
fn_list	additional parameters to pass to the function to estimate GIA

Value

vector of the same size of dose_A and dose_B where each entry is the estimated GIA for the combination of dose A and dose B

Examples

```
model_params <- c("beta_A" = 1, "beta_B" = 2, "gamma_A" = .5,
"gamma_B" = .6, "tau_1" = 1, "tau_2" = 0)
dose_A <- c(0, 1, 0)
dose_B <- c(0, 0, 1)
estimate_GIA(model_params, dose_A, dose_B)
```

estimate_params

Estimate the parameters for a given data set and model

Description

Estimate the parameters for a given data set and model

Usage

```
estimate_params(
  data,
  init_params = c(beta_A = 0.25, beta_B = 0.25, gamma_A = 0.5, gamma_B = 0.5, tau_1 = 0,
  tau_2 = 0),
  n_boot = 100,
  GIA_fn = base_GIA,
  S_fn = calc_S_base,
  fn_list = NULL,
  alpha = 0.05,
  verbose = FALSE
)
```

Arguments

data	data frame with the following columns <ul style="list-style-type: none"> dose_Adose A mg/mL dose_Bdose B mg/mL GIAGIA
init_params	named vector of parameters, that correspond to those used in 'GIA_fn'. These will be used as the initial guesses. A default is provided.
n_boot	number of boot straps to use to estimate confidence intervals of the parameters, GIA estimates, and values of S. The default is 100. If n_boot = 0, then no bootstraps will be run and only the point estimates will be returned.
GIA_fn	function to calculate the GIA from dose_A and dose_B combinations and given set of parameters. Default is base_GIA

S_fn	Function to calculate S. Default is calc_S_base
fn_list	additional arguments to pass to GIA_fn
alpha	alpha level used to produce CIs. The bootstrap will use a two-tailed method. The default is .05 to produce a 95% CI
verbose	logical indicating whether we should print where we are in the process. Default is FALSE.

Value

a list with the following elements

- params_esta data frame of dimension # of params x 4 where each row in the data frame is a parameter and where the columns are the mean, lower, alpha/2 quantile, and upper, 100 - alpha/2 quantile
- S_est a data frame of one row x 4 where we provide the mean, lower, and upper estimates
- GIA_est the original data with additional columns of the mean, lower, and upper estimates for each dose combination
- SSE Sum of Square Error for the model under the best (mean) parameters

Examples

```
df <- loewesadditivity::cyrpa_ripr
df$dose_A <- df$CyRPA
df$dose_B <- df$RIPR
data <- fortify_gia_data(df)
model_params <- c("beta_A" = .5, "beta_B" = .5,
                 "gamma_A" = .5, "gamma_B" = .5,
                 "tau_1" = 0, "tau_2" = 0)

n_boot <- 10
GIA_fn <- base_GIA
S_fn <- calc_S_base
fn_list <- NULL
alpha <- .05
verbose <- FALSE
out <- estimate_params(data = data,
                      init_params = model_params,
                      n_boot = n_boot,
                      GIA_fn = GIA_fn,
                      S_fn = S_fn,
                      fn_list = fn_list,
                      alpha = alpha,
                      verbose = verbose)
names(out)
```

fortify_gia_data	<i>Put GIA measurements into a dplyr format</i>
------------------	---

Description

Put GIA measurements into a dplyr format

Usage

```
fortify_gia_data(data)
```

Arguments

data	data frame of GIA measurements
well	one of "IRBC", "uRBC", "RPMI", or "comb"
dose_A	dose of A in mg/mL
dose_B	dose of B in mg/mL
exp(X)(Y)rep(Z)	where X = 1 or 2, Y = a or b, and Z = 1, 2, or 3

Value

long data frame with columns well, dose_A, dose_B, plate, exp_num (experiment number), plate (a or b), rep_num (repetition number), gia_mean, and average iRBC and uRBC

Examples

```
df <- loewesadditivity::rh5_ama1ron2
df$dose_A <- df$RH5
df$dose_B <- df$AMA1RON2
fortified_df <- fortify_gia_data(df)
head(fortified_df)
```

get_ed_line	<i>Helper function to get the ED50 line</i>
-------------	---

Description

Helper function to get the ED50 line

Usage

```
get_ed_line(
  grid_width = 50,
  par,
  GIA_fn = base_GIA,
  fn_list = NULL,
  ed_val = 50
)
```

Arguments

grid_width	number of levels to find points at
par	named vector of parameters
GIA_fn	function to calculate GIA
fn_list	additional parameters to pass to GIA_fn
ed_val	Which line to compute. Default is 50

Value

data frame with the following columns

dose_A dose of A (unscaled)

dose_B dose of B (unscaled)

GIA value of GIA %

make_grid	<i>Make a grid of points</i>
-----------	------------------------------

Description

Make a grid of points

Usage

```
make_grid(n = 40, par, Amax = 2, Bmax = 2, n_reps = 1)
```

Arguments

n	number of levels on each side (Total grid is n^2). Default is 40
par	named vector of model parameters
Amax	max amount of number of ED50s. Default is 2
Bmax	max amount of number of ED50s. Default is 2.
n_reps	number of replicates to repeat entire grid/experiment. Default is 1.

Value

data frame with the following columns

dose_A unscaled dose of A

dose_B unscaled dose o B

rep replicate number

Examples

```
n <- 40
par <- c("beta_A" = 1, "beta_B" = 2)
out <- make_grid(n = 2, par = par)
exp_out <- data.frame(dose_A = c(0, 2, 0, 2),
                     dose_B = c(0, 0, 4, 4),
                     rep = 1)
```

plot_curves

Plot the surface and observations

Description

Plot the surface and observations

Usage

```
plot_curves(
  est_list,
  dose_A = "Dose A",
  dose_B = "Dose B",
  title = "Curves of Dose Combos",
  subtitle = "",
  base_size = 14
)
```

Arguments

est_list	output from estimate_params
dose_A	to pass to ggplot
dose_B	to pass to ggplot
title	to pass to ggplot
subtitle	to pass to ggplot
base_size	to pass to ggplot

Value

ggplot object

Examples

```
df <- loewesadditivity::cyrpa_ripr
df$dose_A <- df$CyRPA
df$dose_B <- df$RIPR
data <- fortify_gia_data(df)
model_params <- c("beta_A" = .5, "beta_B" = .5,
```

```

      "gamma_A" = .5, "gamma_B" = .5,
      "tau_1" = 0, "tau_2" = 0)
n_boot <- 10
GIA_fn <- base_GIA
S_fn <- calc_S_base
fn_list <- NULL
alpha <- .05
verbose <- FALSE
out <- estimate_params(data = data,
  init_params = model_params,
  n_boot = n_boot,
  GIA_fn = GIA_fn,
  S_fn = S_fn,
  fn_list = fn_list,
  alpha = alpha,
  verbose = verbose)
plots <- plot_curves(out, dose_A = "CyRPA",
  dose_B = "RIPR")

```

plot_isobologram *Plot the estimated isobologram*

Description

Plot the estimated isobologram

Usage

```

plot_isobologram(
  est_list,
  dose_A = "Dose A",
  dose_B = "Dose B",
  GIA_fn = base_GIA,
  fn_list = NULL,
  title = "Isobologram Dose Combos",
  subtitle = "",
  base_size = 14
)

```

Arguments

est_list	output from estimate_params
dose_A	to pass to ggplot
dose_B	to pass to ggplot
GIA_fn	function to calculate GIA
fn_list	additional arguments to pass to GIA fn

title to pass to ggplot
 subtitle to pass to ggplot
 base_size to pass to ggplot

Value

ggplot object

Examples

```

df <- loewesadditivity::cyrpa_ripr
df$dose_A <- df$CyRPA
df$dose_B <- df$RIPR
data <- fortify_gia_data(df)
model_params <- c("beta_A" = .5, "beta_B" = .5,
                  "gamma_A" = .5, "gamma_B" = .5,
                  "tau_1" = 0, "tau_2" = 0)

n_boot <- 10
GIA_fn <- base_GIA
S_fn <- calc_S_base
fn_list <- NULL
alpha <- .05
verbose <- FALSE
out <- estimate_params(data = data,
  init_params = model_params,
  n_boot = n_boot,
  GIA_fn = GIA_fn,
  S_fn = S_fn,
  fn_list = fn_list,
  alpha = alpha,
  verbose = verbose)
plot_curves(out, dose_A = "CyRPA",
  dose_B = "RIPR")

```

plot_surface

Plot the surface and observations

Description

Plot the surface and observations

Usage

```

plot_surface(
  est_list,
  GIA_fn = base_GIA,
  fn_list = NULL,
  xlab = "Dose A",

```

 rh5_ama1ron2

RH5 and AMAIRON2

Description

The data is the raw data for a combination dose of RH5 and AMAIRON2. The data was collected by PEOPLE and on DATE on this GRANT.

Usage

```
rh5_ama1ron2
```

Format

a 38 x 15 data set where the columns are of the following format

well one of iRBC (the max), uRBC (the min), RPMI (??), or comb (which is short for combination)

AMAIRON2 dose of AMAIRON2 in mg/mL

RH5 dose of RH5 in mg/mL

expxyrepz the results from experiment x, sub item y, repetition z

Examples

```
data("rh5_ama1ron2")
head(rh5_ama1ron2)
```

 rh5_rh4

RH5 and RH4

Description

The data is the raw data for a combination dose of RH5 and RH4. The data was originally published in Williams et al. (2018).

Usage

```
rh5_rh4
```

Format

a 48 x 3 data set where the columns are of the following format

RH4 dose of RH4 in mg/mL

RH5 dose of RH5 in mg/mL

GIA Percent Growth inhibition assay averaged over two experiments

Examples

```
data("rh5_rh4")
head(rh5_rh4)
```

simulate_coverage	<i>Simulate a GIA model with an assumed error structure</i>
-------------------	---

Description

Simulate a GIA model with an assumed error structure

Usage

```
simulate_coverage(
  n_sims = 10,
  n_boot = 100,
  verbose = TRUE,
  experimental_grid,
  model_par,
  alpha = 0.05,
  noise_par = c(a0 = 2, a1 = 0.01),
  GIA_fn = base_GIA,
  S_fn = calc_S_base,
  fn_list = NULL
)
```

Arguments

n_sims	number of coverage simulations
n_boot	number of bootstraps to use in each simulation
verbose	logical indicating whether we should use print statements. Default is TRUE
experimental_grid	data frame with columns 'dose_A' and 'dose_B'
model_par	named vector of parameters corresponding to those used in GIA_fn()
alpha	alpha level used to produce confidence intervals for each bootstrap
noise_par	named vector for the noise parameter. Must have names "a0" and "a1". See ?base_gia for more details.
GIA_fn	function used to calculate GIA. Default is base_GIA().
S_fn	function to calculate S
fn_list	additional parameters to pass to GIA_fn

Value

list with the following entries

interaction_cov This is the percent of times 0 was in the $(1-\alpha)\%$ confidence interval for the interaction term "tau_1" from the simulated results

params_cov This is the percent of times the true model parameter (those from model_par) lies in the (marginal) 95% confidence interval for that model parameter.

tau_pos This is the percent of times the $(1-\alpha)\%$ CI of "tau_1" was completely above 0.

tau_neg This is the percent of times $(1-\alpha)\%$ CI of "tau_1" is completely below zero

Examples

```
df <- loewesadditivity::cyrpa_ripr
df$dose_A <- df$CyRPA
df$dose_B <- df$RIPR
data <- fortify_gia_data(df)
model_params <- c("beta_A" = .247, "beta_B" = .224,
                 "gamma_A" = .734, "gamma_B" = .806,
                 "tau_1" = .28, "tau_2" = -.28)
experimental_grid <- make_grid(par = model_params,
                              n = 5)

n_boot <- 100
n_sims <- 10
GIA_fn <- base_GIA
S_fn <- calc_S_base
fn_list <- NULL
alpha <- .05
verbose <- TRUE
## NOT RUN
##out <- simulate_coverage(n_sims = n_sims,
  ##                               n_boot = n_boot,
  ##                               verbose = TRUE,
  ##                               experimental_grid = experimental_grid,
  ##                               model_par = model_params,
  ##                               alpha = .05,
  ##                               noise_par = c("a0" = 3, "a1" = .01),
  ##                               GIA_fn = base_GIA,
  ##                               fn_list = NULL)
##out
```

SSE_GIA

Calculate the Sum of Squared Error

Description

Calculate the Sum of Squared Error

Usage

```
SSE_GIA(par, data, GIA_fn = base_GIA, fn_list = NULL)
```

Arguments

par	named vector of parameters
data	<ul style="list-style-type: none">• dose_Adose A mg/mL• dose_Bdose B mg/mL• GIAGIA
GIA_fn	function to calculate GIA
fn_list	additional arguments to pass GIA_fn

Value

sum of square error between observed and estimated

Index

* datasets

cyrpa_ripr, [5](#)
rh5_ama1ron2, [16](#)
rh5_rh4, [16](#)

base_GIA, [2](#)
boot_GIA, [3](#)

calc_S, [4](#)
calc_S_base, [5](#)
cyrpa_ripr, [5](#)

design_experiment, [6](#)
design_grid, [7](#)

estimate_GIA, [7](#)
estimate_params, [8](#)

fortify_gia_data, [10](#)

get_ed_line, [10](#)

make_grid, [11](#)

plot_curves, [12](#)
plot_isobologram, [13](#)
plot_surface, [14](#)

rh5_ama1ron2, [16](#)
rh5_rh4, [16](#)

simulate_coverage, [17](#)
SSE_GIA, [18](#)