

Package ‘hbim’

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Title Hill/Bliss Independence Model for Combination Vaccines

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Depends R (>= 2.5.0), stats, mvtnorm

Description Calculate expected relative risk and proportion protected assuming normally distributed log10 transformed antibody dose for a several component vaccine. Uses Hill models for each component which are combined under Bliss independence. See Saul and Fay, 2007 <[DOI:10.1371/journal.pone.0000850](https://doi.org/10.1371/journal.pone.0000850)>.

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hbim-package

Hill/Bliss Independence Model for Multicomponent Vaccines

Description

Calculate expected relative risk and proportion protected assuming normally distributed log10 transformed antibody dose for several component vaccine. Uses Hill models for each component which are combined under Bliss independence.

Details

Package: hbim
Type: Package
Version: 1.0
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License: GPL

The hbim package allows users to reproduce plots and calculations for Saul and Fay (2007). See vignette("hbimdetails").

Author(s)

M.P. Fay, Maintainer: Michael Fay <mfay@niaid.nih.gov>

References

Saul A, Fay MP (2007). Human Immunity and the Design of Multi-Component, Single Target Vaccines. PLoS ONE 2(9): e850. doi:10.1371/journal.pone.0000850

calc.foldrange

Calculate standard error and fold-range from confidence interval

Description

Given a confidence interval and sample size, we find the standard error assuming confidence limits are calculated on the log10 responses by either normal confidence limits or t-distribution confidence limits. The fold-range is also output by either methods.

Usage

```
calc.foldrange(n, lower, upper, conf.level = 0.95)
```

Arguments

n	vector of sample size(s) used to create confidence intervals
lower	vector of lower confidence limits
upper	vector of upper confidence limits
conf.level	confidence level, default=.95

Details

See vignette("hbimdetails")

Value

A vector (or matrix) with elements (or columns)

n	sample size
lower	lower confidence limit
upper	upper confidence limit
s.byt	standard deviation assuming confidence intervals calculated by t-distribution
s.byz	standard deviation assuming confidence intervals calculated by normal distribution
foldrange.byt	fold-range assuming confidence intervals calculated by t-distribution
foldrange.byz	fold-range assuming confidence intervals calculated by normal distribution

Examples

```
## sample size=43, lower cl=65, upper cl=85
calc.foldrange(43,65,85)
```

deff.sigma

HBIM data

Description

These 6 data sets were calculated using the associated function. For example, `deff.sigma` was calculated with `eff.sigma`. The 3 data sets that begin with `deff`, give the expected efficacy for several values of μ . The 3 data sets that begin with `dpp` give the percent protected with several values of μ . The data sets that end in `.sigma` change for different values of σ , and similarly for `.mu` and `.rho` (see `deff.sigma`).

Usage

```
data(deff.sigma)
data(deff.mu)
data(deff.rho)
data(dpp.sigma)
data(dpp.mu)
data(dpp.rho)
```

Format

The format is: List of 8

- mu vector of different values of mean for log10 antibody
- out1matrix of either expected efficacy or percent protected for 1 component model, rows correspond to mu, cols correspond to cparms
- out2matrix of either expected efficacy or percent protected for 2 component model, rows correspond to mu, cols correspond to cparms
- out3matrix of either expected efficacy or percent protected for 3 component model, rows correspond to mu, cols correspond to cparms
- col1vector of colors for different cparms of 1 component model
- col2vector of colors for different cparms of 2 component model
- col3vector of colors for different cparms of 3 component model
- cparmsvector parameters that change

Examples

```
## here is the code that produces the 6 data sets, it takes about 25 hours to run
## so it is commented out here
#NSIM<-5*10^5
#SIGMAS.POWER<-c(9,65,5000)
#SIGMAS<-log10(SIGMAS.POWER)/(2*qnorm(.975))
#SCOLORS<-c("green","blue","red")
#FACTORS<-c(1/10, 1/3, 1/2, 1)
#FCOLORS<-c("red", "green", "blue", "black")
#RHOS<-c(-.5,-.25,0, 0.25, 0.5, 0.75, 1)
#RCOLORS<- c("black","tan","yellow","blue", "green", "red", "black")
#set.seed(1234521)
#MU<-((-40:40)/10)
#deff.sigma<-eff.sigma(mu=MU, sigmas=SIGMAS, COLORS = SCOLORS, rho = 0)
#deff.mu<-eff.mu(mu=MU, factor = FACTORS, COLORS = FCOLORS, sigma = SIGMAS[2], rho = 0)
#deff.rho<-eff.rho(mu=MU, sigma = SIGMAS[2], rho = RHOS, COLORS =RCOLORS,simulate=TRUE,nsim=NSIM)
#set.seed(32401)
#dpp.sigma<-pp.sigma(MU,sigmas=SIGMAS,COLORS = SCOLORS, rho = 0,nsim=NSIM)
#set.seed(21345123)
#dpp.mu<-pp.mu(MU,factor = FACTORS, COLORS = FCOLORS, sigma = SIGMAS[2], rho = 0, nsim=NSIM)
#set.seed(435919)
#dpp.rho<-pp.rho(MU,sigma = SIGMAS[2], rho = RHOS, COLORS =RCOLORS,nsim=NSIM)
```

Description

These functions create the data sets used in the plots. The first part of the name denotes the output created. Thus, `eff.sigma`, `eff.mu`, `eff.rho` create efficacy values, while `pp.sigma`, `pp.mu`, `pp.rho` create percent protected values. The second part of the name is the parameter which is changed. For example, `eff.sigma` creates efficacy values for different values of sigma. See details for a more complete description. Default for `eff.` functions is integration, default for `pp.` functions is simulation.

Usage

```
eff.sigma(mu, sigmas, COLORS = c("red", "green", "blue"),
  rho = 0, ...)
eff.mu(mu, factor = c(1/10, 1/3, 1/2, 1),
  COLORS = c("red", "green", "blue", "black"),
  sigma = 0.553, rho = 0, ...)
eff.rho(mu, sigma = 0.553, rho = c(0, 0.25, 0.5, 0.75, 1),
  COLORS = c("black", "blue", "green", "red", "black"), ...)
pp.sigma(mu, sigmas, COLORS = c("red", "green", "blue"),
  rho = 0, nsim = 10^5)
pp.mu(mu, factor = c(1/10,1/3,1/2,1),
  COLORS = c("red", "green", "blue", "black"),
  sigma = 0.553, rho = 0, nsim = 10^5)
pp.rho(mu, sigma = 0.553, rho = c(0, 0.25, 0.5, 0.75, 1),
  COLORS = c("black", "blue", "green", "red", "black"),
  nsim = 10^5)
```

Arguments

<code>mu</code>	a vector of values of the mean of the log10 antibody
<code>factor</code>	a vector of values for defining the means of the second and third component (see details and warnings)
<code>COLORS</code>	colors for the plots, the <i>i</i> th color corresponds to the <i>i</i> th value of the parameter which is changing
<code>sigmas</code>	a vector of values of the standard deviation of the log10 antibody
<code>sigma</code>	a single value for sigma
<code>rho</code>	correlation vector (of length one for <code>.sigma</code> and <code>.mu</code> functions) of the log10 antibody, negative values not allowed
<code>nsim</code>	number of simulations for <code>hbpp</code> function
<code>...</code>	additional parameters may be added to the <code>hbrr</code> function

Details

For `eff.sigma` and `pp.sigma` we change sigma over the one, two, and three component model. For `eff.mu` and `pp.mu` we change the mean over the two and three component model. For `eff.mu` and `pp.mu` the factor parameter is associated with each level of the second and third component. See `vignette("hbimdetails")` for details. For `eff.rho` and `pp.rho` we change the correlation over

the two and three component model; for the j th column of the out2 and out3 matrices, all correlations are given by j th level of factor. Because these calculations may take hours, we save the original calculations used in the paper as output data, `deff.sigma`, `deff.mu`, `deff.rho`, `dpp.sigma`, `dpp.mu`, and `dpp.rho`. These output data set may be accessed by the command `data()`. For example, to access `deff.sigma` type `data(deff.sigma)`.

Value

A list with items

out1	response matrix for one component model, i th row corresponds to $\mu[i]$ and j th column corresponds to the j th level of the parameter which is changing
col1	colors corresponding to columns of out1
out2	response matrix for two component model, i th row corresponds to $\mu[i]$ and j th column corresponds to the j th level of the parameter which is changing
col2	colors corresponding to columns of out2
out3	response matrix for three component model, i th row corresponds to $\mu[i]$ and j th column corresponds to the j th level of the parameter which is changing
col3	colors corresponding to columns of out3
cparms	input vector of parameter that changes, e.g., factor vector
sigma	input sigma
rho	input rho

Warning

Note to save computation time these functions do not check that all variance-covariance matrices used in the internal functions are positive definite. If you get an error message you do not understand check to see if the variance-covariance matrix is positive definite by checking the eigen values. For example, with $\sigma=1$, $\rho=-.6$, the 3 components model do not have a positive definite variance-covariance matrix because there is a negative eigenvalue (to see this run `eigen(make.v(3, -.6, 1))`).

Author(s)

M.P. Fay

See Also

`vignette("hbimdetails")`

`equiv.ab`*Equivalent antibody calculations by Linear Interpolation*

Description

This function inputs two antibody by response curves and outputs values needed for plots of equivalent antibody response. This is called by other functions ([plotresp.equiv](#), [plotresp.mix](#)). It is not to be called directly. For that purpose use [equiv.increase](#).

Usage

```
equiv.ab(effab1, ab1, effab2, ab2, npts = 100)
```

Arguments

<code>effab1</code>	vector of responses for antibody 1
<code>ab1</code>	vector of doses of antibody 1
<code>effab2</code>	vector of responses for antibody 2
<code>ab2</code>	vector of doses of antibody 2
<code>npts</code>	number of points used in some output

Details

The function uses the [approx](#) function to do linear interpolation and find the needed values.

Value

A list containing:

<code>abpts</code>	a vector of values of antibody dose
<code>abpts10</code>	antilog of abpts, i.e., abpts raised to tenth power
<code>equiv.eff2</code>	equivalent response of antibody 2
<code>equiv.eff1</code>	equivalent response of antibody 1
<code>equiv.ab1</code>	vector of antibody doses that correspond with equiv.eff1
<code>x</code>	<code>equiv.ab1-abpts</code>
<code>y</code>	<code>equiv.eff1</code>

See Also

[equiv.increase](#)

equiv.increase *Calculate equivalent increase from two dose-response curves*

Description

This function takes two curves defined by vectors of x and y values and calculates the equivalent increase in the x value at the response value for the first curve at e1.

Usage

```
equiv.increase(x1, y1, x2, y2, e1, xlog = TRUE)
```

Arguments

x1	x vector for first curve
y1	y vector for first curve
x2	x vector for second curve
y2	y vector for second curve
e1	vector of y responses of first curve for associating with output
xlog	TRUE if x values are log transformed, changes the output

Details

The function repeatedly uses the [approx](#) function to do linear interpolation.

Value

A list with 5 components

a1	vector of x values associated with e1 from first curve
e2	vector of y values associated with a1 from the second curve
a2	vector of x values associated with e2 from the second curve
e1	input vector for e1
equiv.increase	vector of equivalent increases associated with e1

Examples

```
data(deff.sigma)
D<-deff.sigma
equiv.increase(D$mu,D$out1[,2],D$mu,D$out2[,2],.5)
```

hbr	<i>Calculate expected relative risk or percent protected from Hill model with Bliss Independence</i>
-----	--

Description

Assuming that the log10 transformed doses are normally distributed, we calculate the expected relative risk (using hbr) or percent protected (using hbpp) from the Hill model using Bliss Independence. Numeric integration is the default for up to three components for hbr, while simulation is the default for two or three components for hbpp.

Usage

```
hbr(mu, v, a = rep(1, length(mu)), simulate = FALSE, nsim = 10^4, ...)
hbpp(mu, v, a = rep(1, length(mu)), rp = 0.1, simulate = FALSE, nsim = 10^5, ...)
```

Arguments

mu	mean vector of the log10 dose
v	variance matrix of the log10 dose
a	vector of slope parameters in the Hill model, one for each component
simulate	estimation by simulation (TRUE) or numeric integration (FALSE)
nsim	number of simulations, ignored if simulate=FALSE
rp	protection bound, an individual is protected if relative risk is greater than rp
...	additional parameters to pass to the integrate function

Details

Although the package adapt can do multidimensional integration, we have written specific functions to do this for up to 3 dimensions. This allows faster and more accurate integration. The integration is done by repeated calls to the `integrate` function. The functions which do the actual integration or simulation are internal functions which are not intended to be called by the user. These internal functions are: for hbr, when simulate=FALSE, the function calls one of either `hbr.integrate1`, `hbr.integrate2`, `hbr.integrate2.rhoeq1`, `hbr.integrate3`, or `hbr.integrate3.rhoeq1` (for 1,2, or 3 component, with or without rho=1, taken from the size of the mu vector and dimension of the v matrix) and when simulation=TRUE it calls `hbr.simulate`. Similar functions exist for hbpp; however, the `hbpp.integrate2` and `hbpp.integrate3` may have problems because of the discontinuity in the integration function. That is why for two or three component models `hbpp.simulate` is used by default.

Value

a numeric value of the expected relative risk or percent protected.

Author(s)

M.P. Fay

References

Saul A, Fay MP (2007). Human Immunity and the Design of Multi-Component, Single Target Vaccines. PLoS ONE 2(9): e850. doi:10.1371/journal.pone.0000850

Examples

```
## example of two dimensional integral
hbr(c(.123,.432),matrix(c(1,.5,.5,1),2,2))
## faster but less accurate estimation by simulation
hbr(c(.123,.432),matrix(c(1,.5,.5,1),2,2),simulate=TRUE,nsim=10^4)
```

 irdata

Immune Response data

Description

Data from literature.

Usage

```
data(irdata)
```

Format

A data frame with 574 observations on the following 16 variables.

RecordNum a numeric vector

Old.Reference a numeric vector

Reference a numeric vector

Vaccine.and.trial.group a factor with levels (Pentacel +Recombivax) then Prevnar 11 valent Pneumococcal-DT Finland 11 valent Pneumococcal-DT Israel 11 valent Pneumococcal-DT+alum Finland 11 valent Pneumococcal-DT+alum Israel 11 valent Pneumococcal-DT+alum Philippines ACTHIB AP-YF AVA IM AVA SQ BERNA-YF Boostrix Boostrix + Poliorix Boostrix Polio (dTpa-IPV) DPAT-HVB-IPV/HIB mix DPAT-HVB-IPV+HIB separate DPAT-IPV/HiB mix DPAT-IPV+HiB separately DPT +Hib/HBV DPT +Hib + HBV DPTa DPTa/Pa DPTa5 DT DTP-HB + Hib DTPa-HBV DTPa/IPV/PRP-TT +PncD/T11 DTPa2 DTPa3 DTPa5 DTPaHBV-IPV+Hib DTPaHBV-IPV+Hib, PRP DTPaHBV-IPV+Hib, PRP-TT DTPw-C DTPw-E DTPw/IPV/PRP-TT +PncD/T11 group 1 DTPw/IPV/PRP-TT +PncD/T11 group 2 DTPwHBV-Hib DTPwHBV + Hib(Separate) Engerix B GBS Ia-TT 15 ug GBS Ia-TT 3.75 ug GBS Ia 55 ug GBS IaTT 60 ug GBS Ib-TT 15.75 ug GBS Ib-TT 3.94 ug GBS Ib-TT 63 ug GBS Ib 53 ug GBS II-TT GBS II-TT 14.3 ug GBS II-TT 3.6 ug GBS II-TT 57 ug GBS II-TT/III-TT GBS III-TT GBS III-TT 14.5 ug GBS III-TT 3.6 ug GBS III-TT 58 ug GBS

III 50 ug GBS V-CRM197 GBS V-TT GBS V-TT 2.4/1.1 ug GBS V-TT 38.5/17 ug GBS V-TT 9.6/4.3
 ug H5N1Influenza 45ug H5N1Influenza 7.5ug H5N1Influenza 90ug H5N1Influenza 15ug
 H5N1Influenza Placebo Havrix+Engerix B HBV/Pentavax Heptavalent Pneumococcal-CRM197
 Heptavalent Pneumococcal-OMPC Heptavalent Pneumococcal-CRM197 Hiberix HibTITER
 HibTITER (PRP-CRM197) Infanrix-IVP+Hib Infanrix-IVP+Hib+Previnar Infanrix
 + Engerix separate Infanrix/Engerix Mixed Infanrix/Engerix Mixed IPV-mk IPV-vero
 Lyme OspA 15ug Lyme OspA 30ug LYMERix (OpsA) MCV4-DT Menactra Meningococcal PS-DT
 (MCV-4) Mencevax ACWY Meningitec (Menc-CRM197) Menomune Meningococcal PS Menomune
 Meningococcal PS (PSV-4) Octavalent Pneumococcal-DT Octavalent Pneumococcal-TT
 Oka/Merck varicella 16K PFU +M-M-R Oka/Merck varicella 50K PFU +M-M-R OpsA Lyme Disease
 Orimmune OspA Lyme Pentacel + Prevna +Recombivax Pentavax Revaxis (Td-IPV) RKI-YF
 RSV PFP3 Tripedia Tripedia-Orimune-HibTITER Twinrix Twinrix adult Twinrix pediatric
 Typhoid/HAV Varilrix + M-M-R

Carrier.for.conjugate.vaccines a factor with levels CRM197 Diphtheria toxoid OMPC Tetanus
 protein Tetanus toxoid

Age.in.yrs.at.first.vaccination a factor with levels 0.12 0.17 0.17-0.5 0.25 0.5 1 1-12
 1-2 1.5 11-18 12-15 15-18 15-70 16-65 17-72 18-32 18-39 18-40 18-45 18-50 18-60
 18-64 19-52 19-56 19-57 19-64 19-70 19-83 2 2-5 20-45 20-60 20-61 21-60 3 4 4-14
 40-70 5-16 65-83

Dose.schedule.in.weeks a factor with levels 0 0, 2 0, 2, 4 0, 26 0, 26/0, 4, 26 0, 4 0, 4, 10
 0, 4, 26 0, 4, 52 0, 4, 8 0, 4, 8, 52 0, 52 0, 52, 104 0, 6, 13 0, 8 0, 8, 16 0, 8, 18 0,
 8, 18 0, 8, 18, 220 0, 8, 18, 270 0, 8, 18, 320 0, 8, 18, 44 0, 8, 18, 56 0, 8, 18, 60
 0, 8, 18, 70 0, 8, 18; 4,12,22 0, 8, 18; 4,12,22 0, 8, 39 0, 9, 37

Num.Immunizations a numeric vector

Endpoint.in.weeks.after.first.vaccine a numeric vector

Antigen a factor with levels 1 14 18C 19F 23F 3 4 5 6B 7F 9V A AVA C DT F protein FHA FIM HAV
 HBs Hemagglutinin Ia-CPS Ib-CPS II-CPS III-CPS Measles MenC Mumps OspA Polio-1
 Polio-2 Polio-3 PRN PRP PRP* PT Rubella TT V-CPS Varicella Vi W135 Y YF

Units a factor with levels EL.U/mL EU HI IU mIU ng SBA ug

GMT a numeric vector

GMT.95.pct.interval.low.limit a numeric vector

GMT.95.pct.interval.high.limit a numeric vector

n a numeric vector

Fold.Range a numeric vector

Source

See data(refs) for references

Examples

```
data(irdata)
irdata[1,]
```

make.v	<i>Make Exchangeable Variance Matrix</i>
--------	--

Description

Not to be called directly. Used by `eff.sigma`, `eff.mu`, `eff.rho`, `pp.sigma`, `pp.mu`, and `pp.rho`.

Usage

```
make.v(n, r, sig2)
```

Arguments

n	dimension of variance matrix
r	correlation
sig2	variance

Value

An variance-covariance matrix, with all diagonal elements equal and all off diagonal elements equal.

plotlogm.resp	<i>Plot Hill/Bliss Independence Model Data.</i>
---------------	---

Description

These functions take data output calculated from the data generating functions (see details) and plot either: the mean of the log transformed antibody doses by the response (`plotlogm.resp`), equivalent increase in antibody plots (`plotresp.equiv`), or response of one component versus a mixture (for details see `vignette("hbimdetails")`).

Usage

```
plotlogm.resp(D, YLAB = "Efficacy", YLIM = c(0, 1),
  XLIM = c(-2, 2),TITLE="")
plotresp.equiv(D, XLIM = c(0, 1), YLIM = c(1, 100),
  RLAB = "Efficacy of", bounds= XLIM,TITLE="")
plotresp.mix(D, RLAB = "Efficacy of", XYLIM = c(0, 1),TITLE="")
```

Arguments

D	data, see details
YLAB	y label
YLIM	range of y axis
XLIM	range of x axis
RLAB	response label, currently use only either "Efficacy of" or "% Protected by"
bounds	bounds on response of second antibody curve, see <code>vignette("hbimdetails")</code>
XYLIM	range of both x and y axes
TITLE	title of plot

Details

The following functions create data sets for plotting: `eff.sigma`, `eff.mu`, `eff.rho`, `pp.sigma`, `pp.mu`, `pp.rho`. These functions plot that data. For details see `vignette("hbimdetails")`.

Value

Plots

refs

Reference list

Description

Each reference is one long character string. See `data(irdata)` for data from each reference.

Usage

```
data(refs)
```

Format

The format is: Factor w/ 50 levels (the 50 references)

Examples

```
data(refs)
refs[1]
```

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