

Package ‘c212’

July 22, 2025

Type Package

Title Methods for Detecting Safety Signals in Clinical Trials Using Body-Systems (System Organ Classes)

Version 1.0.1

Date 2024-11-04

Author Raymond Carragher [aut, cre] (ORCID:
<<https://orcid.org/0000-0002-0120-625X>>)

Depends coda (>= 0.19)

Encoding UTF-8

LazyData true

Description Provides a self-contained set of methods to aid clinical trial safety investigators, statisticians and researchers, in the early detection of adverse events using groupings by body-system or system organ class. This work was supported by the Engineering and Physical Sciences Research Council (UK) (EPSRC) [award reference 1521741] and Frontier Science (Scotland) Ltd. The package title c212 is in reference to the original Engineering and Physical Sciences Research Council (UK) funded project which was named CASE 2/12.

License GPL-3

URL <https://github.com/rcarragh/c212>

BugReports <https://github.com/rcarragh/c212/issues>

NeedsCompilation yes

Maintainer Raymond Carragher <rcarragh@gmail.com>

Repository CRAN

Date/Publication 2024-11-05 22:00:03 UTC

Contents

c212-package	3
c212.1a	4

c212.1a.interim	7
c212.BB	11
c212.BB.interim	15
c212.BH	19
c212.BH.adjust.pvals	21
c212.bin.test	23
c212.BONF	24
c212.convergence.diag	25
c212.DFDR	27
c212.err.cnt1	28
c212.FDR.data	29
c212.fisher.test	30
c212.GBH	31
c212.gen.initial.values	32
c212.global.sim.params	33
c212.hyper.params	34
c212.interim.1a.hier2	35
c212.interim.1a.hier3	39
c212.interim.BB.hier2	42
c212.interim.BB.hier3	46
c212.interim.MLE	50
c212.LSL	51
c212.monitor.samples	52
c212.NOADJ	53
c212.plot.eot.data	54
c212.plot.interim.data.rd	55
c212.plot.samples	56
c212.pointmass.weights	57
c212.print.convergence.summary	58
c212.print.summary.stats	59
c212.ptheta	60
c212.sim.control.params	61
c212.ssBH	62
c212.summary.stats	63
c212.trial.data	64
c212.trial.interval.data1	65
c212.trial.interval.data2	65
c212.TST	66
Index	68

Description

This package implements a number of methods for the detection of safety signals in Clinical Trials based on groupings of adverse events by body-system or system organ class. The methods include an implementation of the Three-Level Hierarchical model for Clinical Trial Adverse Event Incidence Data of Berry and Berry (2004) and an implementation of the same model without the Point Mass (Model 1a from Xia et al (2011)), extended Bayesian hierarchical methods based on system organ class or body-system groupings for interim analyses. The package also implements a number of methods for error control when testing multiple hypotheses, specifically control of the False Discovery Rate (FDR). The FDR control methods implemented are the Benjamini-Hochberg procedure, the Double False Discovery Rate, the Group Benjamini-Hochberg and subset Benjamini-Hochberg methods. Also included are the Bonferroni correction and the unadjusted testing procedure.

Details

The methods implemented use assumed groupings of adverse events by body-system or system organ class to detect differences in the occurrence of adverse events on trial arms. Methods based on Bayesian Hierarchical models and direct error controlling procedures are provided.

The basic (Bayesian) hierarchical models are described in Berry and Berry (2004), Xia et al (2011) (Model 1a) and Berry et al (2010). These methods are extended for interim analyses.

The direct error controlling methods are designed to control the number of Type-I errors at an acceptable level without compromising the power. If the Familywise Error Rate (FWER) is defined as the probability of making one or more Type-I errors when analysing multiple hypotheses (the “family”), then an alternative to controlling the FWER is to control the False Discovery Rate (FDR) - the expected proportion of false discoveries (Type-I errors) to the total number of discoveries. Essentially control of the FDR assumes that when many of the tested hypotheses are rejected it may be preferable to control the proportion of errors rather than the probability of making even one error. This is expected to lead to a gain in power. Further FDR controlling methods which use the information available in groupings of hypotheses have been developed (Double False Discovery Rate (Mehrotra and Adewale (2012)), Group Benjamini-Hochberg (Hu, Zhao and Zhou (2010))). For the methods contained in this package control of the False Discovery Rate has been established for independent test statistics and some forms of positive dependency (positive regression dependency), apart from the case of the Group Benjamini-Hochberg procedure where the control is asymptotic. Further details can be found in the references.

Author(s)

R. Carragher<raymond.carragher@strath.ac.uk; rcarragh@gmail.com>

References

S. M. Berry and D. A. Berry (2004). Accounting for multiplicities in assessing drug safety: a three-level hierarchical mixture model. *Biometrics*, 60(2):418-26.

- H. Amy Xia, Haijun Ma, and Bradley P. Carlin (2011). Bayesian hierarchical modelling for detecting safety signals in clinical trials. *Journal of Biopharmaceutical Statistics*, 21(5):1006–1029.
- Scott M. Berry, Bradley P. Carlin, J. Jack Lee, and Peter Müller (2010). *Bayesian adaptive methods for clinical trials*. CRC Press.
- Benjamini, Yoav and Hochberg, Yosef, (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, 57(1):289-300.
- D. V. Mehrotra and J. F. Heyse (2004). Use of the false discovery rate for evaluating clinical safety data. *Stat Methods Med Res*, 13(3):227–38, 2004.
- Mehrotra, D. V. and Adewale, A. J. (2012). Flagging clinical adverse experiences: reducing false discoveries without materially compromising power for detecting true signals. *Stat Med*, 31(18):1918-30.
- Hu, J. X. and Zhao, H. and Zhou, H. H. (2010). False Discovery Rate Control With Groups. *J Am Stat Assoc*, 105(491):1215-1227.
- Y. Benjamini, A. M. Krieger, and D. Yekutieli (2006). Adaptive linear step-up procedures that control the false discovery rate. *Biometrika*, 93(3):491–507.
- Benjamini Y, Hochberg Y. (2000). On the Adaptive Control of the False Discovery Rate in Multiple Testing With Independent Statistics. *Journal of Educational and Behavioral Statistics*, 25(1):60–83.
- Yekutieli, Daniel (2008). False discovery rate control for non-positively regression dependent test statistics. *Journal of Statistical Planning and Inference*, 138(2):405-415.
- Matthews, John N. S. (2006) *Introduction to Randomized Controlled Clinical Trials*, Second Edition. Chapman & Hall/CRC Texts in Statistical Science.

c212.1a

Implementation of the Berry and Berry Three-Level Hierarchical Model without Point-Mass.

Description

Implementaion of Berry and Berry model without the point-mass (Model 1a Xia et al (2011))

Usage

```
c212.1a(trial.data, sim_type = "SLICE", burnin = 10000, iter = 40000,
nchains = 3,
global.sim.params = data.frame(type = c("MH", "SLICE"),
param = c("sigma_MH", "w"),
value = c(0.35,1), control = c(0,6), stringsAsFactors = FALSE),
sim.params = NULL,
initial_values = NULL,
hyper_params = list(mu.gamma.0.0 = 0, tau2.gamma.0.0 = 10,
mu.theta.0.0 = 0, tau2.theta.0.0 = 10, alpha.gamma.0.0 = 3,
beta.gamma.0.0 = 1, alpha.theta.0.0 = 3, beta.theta.0.0 = 1,
alpha.gamma = 3, beta.gamma = 1,
alpha.theta = 3, beta.theta = 1))
```

Arguments

<code>trial.data</code>	A file or data frame containing the trial data. It must contain must contain the columns <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants in the trial arm).
<code>sim_type</code>	The type of MCMC method to use for simulating from non-standard distributions. Allowed values are "MH" and "SLICE" for Metropolis_Hastings and Slice sampling respectively.
<code>burnin</code>	The burnin period for the monte-carlo simulation. These are discarded from the returned samples.
<code>iter</code>	The total number of iterations for which the monte-carlo simulation is run. This includes the burnin period. The total number of samples returned is <i>iter - burnin</i>
<code>nchains</code>	The number of independent chains to run.
<code>global.sim.params</code>	A data frame containing the parameters for the simulation type <i>sim_type</i> . For "MH" the parameter is the variance of the normal distribution used to simulate the next candidate value centred on the current value. For "SLICE" the parameters are the estimated width of the slice and a value limiting the search for the next sample.
<code>sim.params</code>	A dataframe containing simulation parameters which override the global simulation parameters (<i>global.sim.params</i>) for particular model parameters. <i>sim.params</i> must contain the following columns: type: the simulation type ("MH" or "SLICE"); variable: the model parameter for which the simulation parameters are being overridden; B: the body-system (if applicable); AE: the adverse event (if applicable); param: the simulation parameter; value: the overridden value; control: the overridden control value. The function <i>c212.sim.control.params</i> generates a template for <i>sim.params</i> which can be edited by the user.
<code>initial_values</code>	The initial values for starting the chains. If NULL (the default) is passed the function generates the initial values for the chains. <i>initial_values</i> is a list with the following format: <pre>list(gamma, theta, mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0)</pre> <p>where each element of the list is either a dataframe or array. The function <i>c212.gen.initial.values</i> can be used to generate a template for the list which can be updated by the user if required. The formats of the list elements are as follows:</p> <p><i>gamma, theta</i>: dataframe with columns <i>B, AE, chain, value</i> <i>mu.gamma, mu.theta, sigma2.gamma, sigma2.theta</i>: dataframe with columns <i>B, chain, value</i> <i>mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0</i>: array of size <i>chain</i>.</p>
<code>hyper_params</code>	The hyperparameters for the model. The default hyperparameters are those given in Berry and Berry 2004.

Details

The model is fitted by a Gibbs sampler. The details of the complete conditional densities are given in Berry and Berry (2004). The posterior distributions for *gamma* and *theta* are sampled with either a Metropolis-Hastings step or a slice sampler.

Value

The output from the simulation including all the sampled values is as follows:

```
list(id, sim_type, chains, nBodySys, maxAEs, nAE, AE, B, burnin,
iter, mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0,
mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, gamma,
theta, gamma_acc, theta_acc)
```

where

id - a string identifying the version of the function

sim_type - an string identifying the sampling method used for non-standard distributions, either "MH" or "SLICE"

chains - the number of chains for which the simulation was run

nBodySys - the number of body-systems

maxAEs - the maximum number of AEs in a body-system

nAE - an array. The number of AEs in each body-system.

AE - an array of dimension *nBodySys*, *maxAEs*. The Adverse Events.

B - an array. The body-systems.

burnin - the burnin period for the simulation.

iter - the total number of iterations in the simulation.

mu.gamma.0 - array of samples of dimension *chains*, *iter* - *burnin*

mu.theta.0 - array of samples of dimension *chains*, *iter* - *burnin*

tau2.gamma.0 - array of samples of dimension *chains*, *iter* - *burnin*

tau2.theta.0 - array of samples of dimension *chains*, *iter* - *burnin*

mu.gamma - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

mu.theta - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

sigma2.gamma - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

sigma2.theta - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

gamma - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*

theta - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*

gamma_acc - the acceptance rate for the gamma samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

theta_acc - the acceptance rate for the theta samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

Note

The function performs the simulation and returns the raw output. No checks for convergence are performed.

Author(s)

R. Carragher

References

S. M. Berry and D. A. Berry (2004). Accounting for multiplicities in assessing drug safety: a three-level hierarchical mixture model. *Biometrics*, 60(2):418-26.

H. Amy Xia, Haijun Ma, and Bradley P. Carlin (2011). Bayesian hierarchical modelling for detecting safety signals in clinical trials. *Journal of Biopharmaceutical Statistics*, 21(5):1006– 1029.

Scott M. Berry, Bradley P. Carlin, J. Jack Lee, and Peter M"ller (2010). *Bayesian adaptive methods for clinical trials*. CRC Press.

Examples

```
data(c212.trial.data)
raw = c212.1a(c212.trial.data, burnin = 100, iter = 200)
## Not run:
data(c212.trial.data)
raw = c212.1a(c212.trial.data)

raw$B
[1] "Bdy-sys_1" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5" "Bdy-sys_6"
[7] "Bdy-sys_7" "Bdy-sys_8"

mean(rm$theta[2, 3,1,])
[1] 1.306362

## End(Not run)
```

c212.1a.interim

A Two or Three-Level Hierarchical Body-system based Model for interim analysis without Point-Mass.

Description

Implementation of a Two or Three-Level Hierarchical Body-system based Model for interim analysis without Point-Mass.

Usage

```
c212.1a.interim(trial.data, sim_type = "SLICE", burnin = 10000,
  iter = 40000, nchains = 3,
  global.sim.params = NULL,
  sim.params = NULL,
  monitor = NULL,
  initial_values = NULL,
  hier = 3,
  level = 1,
  hyper_params = NULL,
  memory_model = "HIGH")
```

Arguments

trial.data	A file or data frame containing the trial data. It must contain must contain the columns <i>I_index</i> (interval index), <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants in the trial arm).
sim_type	The type of MCMC method to use for simulating from non-standard distributions. Allowed values are "MH" and "SLICE" for Metropolis_Hastings and Slice sampling respectively.
burnin	The burnin period for the monte-carlo simulation. These are discarded from the returned samples.
iter	The total number of iterations for which the monte-carlo simulation is run. This includes the burnin period. The total number of samples returned is <i>iter - burnin</i>
nchains	The number of independent chains to run.
global.sim.params	A data frame containing the parameters for the simulation type <i>sim_type</i> . For "MH" the parameter is the variance of the normal distribution used to simulate the next candidate value centred on the current value. For "SLICE" the parameters are the estimated width of the slice and a value limiting the search for the next sample. Passing NULL uses the model defaults.
sim.params	A dataframe containing simulation parameters which override the global simulation parameters (<i>global.sim.params</i>) for particular model parameters. <i>sim.params</i> must contain the following columns: type: the simulation type ("MH" or "SLICE"); variable: the model parameter for which the simulation parameters are being overridden; B: the body-system (if applicable); AE: the adverse event (if applicable); param: the simulation parameter; value: the overridden value; control: the overridden control value. Passing NULL uses the model defaults. The function <i>c212.sim.control.params</i> generates a template for <i>sim.params</i> which can be edited by the user.
monitor	A dataframe indicating which sets of If NULL is passed default parameters are variables to monitor. Passing NULL uses the model defaults.
initial_values	The initial values for starting the chains. If NULL (the default) is passed the function generates the initial values for the chains. <i>initial_values</i> is a list with the following format:


```
list(gamma, theta, mu.gamma, mu.theta, sigma2.gamma,
     sigma2.theta, mu.gamma.0, mu.theta.0, tau2.gamma.0,
     tau2.theta.0)
```

where each element of the list is either a dataframe or array. The function *c212.gen.initial.values* can be used to generate a template for the list which can be updated by the user if required. The formats of the list elements are as follows:

gamma, theta: dataframe with columns *B, AE, chain, value*

mu.gamma, mu.theta, sigma2.gamma, sigma2.theta: dataframe with columns *B, chain, value*

mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0: array of size *chain*.

hier	Model using a two or three level hierarchy. 2 - two-level hierarchy, 3 - three level hierarchy.
level	The level of longitudinal dependency between the intervals. Allowed values are 0, 1, 2 for a three-level hierarchy and 0, 1 for a two-level hierarchy. 0 - independent intervals, 1 - common interval body-system means, 2 - weak dependency.
hyper_params	The hyperparameters for the model. The default hyperparameters are based on those given in Berry and Berry 2004. Passing NULL uses the model defaults.
memory_model	Allowed values are "HIGH" and "LOW". "HIGH" means use as much memory as possible. "LOW" means use the minimum amount of memory.

Details

The models are fitted by Gibbs samplers. The posterior distributions for *gamma* and *theta* are sampled with either a Metropolis-Hastings step or a slice sampler.

Value

The output from the simulation including all the sampled values for the three-level hierarchy is as follows:

```
list(id, sim_type, chains, nIntervals, Intervals, nBodySys, maxBs,
     maxAEs, nAE, AE, B, burnin, iter, monitor,
     mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0,
     mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, gamma,
     theta, gamma_acc, theta_acc)
```

The output from the simulation including all the sampled values for the two-level hierarchy is as follows:

```
list(id, sim_type, chains, nIntervals, Intervals, nBodySys, maxBs,
     maxAEs, nAE, AE, B, burnin, iter, monitor,
     mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, gamma,
     theta, gamma_acc, theta_acc)
```

where

id - a string identifying the version of the function

sim_type - an string identifying the sampling method used for non-standard distributions, either "MH" or "SLICE"

chains - the number of chains for which the simulation was run.

nIntervals - the number of intervals in the simulation

Intervals - an array. The intervals.

nBodySys - the number of body-systems

maxBs - the maximum number of body-systems in an interval

maxAEs - the maximum number of AEs in a body-system

nAE - an array. The number of AEs in each body-system.

AE - an array of dimension *nBodySys*, *maxAEs*. The Adverse Events.

B - an array. The body-systems.

burnin - burnin used for the simulation.

iter - the total number of iterations in the simulation.

monitor - the variables being monitored. A dataframe.

mu.gamma.0 - array of samples of dimension *chains*, *iter* - *burnin*

mu.theta.0 - array of samples of dimension *chains*, *iter* - *burnin*

tau2.gamma.0 - array of samples of dimension *chains*, *iter* - *burnin*

tau2.theta.0 - array of samples of dimension *chains*, *iter* - *burnin*

mu.gamma - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

mu.theta - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

sigma2.gamma - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

sigma2.theta - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

gamma - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*

theta - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*

gamma_acc - the acceptance rate for the gamma samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

theta_acc - the acceptance rate for the theta samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

Note

The function performs the simulation and returns the raw output. No checks for convergence are performed.

Author(s)

R. Carragher

Examples

```

data(c212.trial.interval.data1)
raw = c212.1a.interim(c212.trial.interval.data1, burnin = 100, iter = 200)
## Not run:
data(c212.trial.interval.data1)
raw = c212.1a.interim(c212.trial.interval.data1)

raw$B
      [,1]      [,2]      [,3]      [,4]      [,5]
[1,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[2,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[3,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[4,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[5,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[6,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
      [,6]      [,7]      [,8]      [,9]     [,10]     [,11]
[1,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[2,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[3,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[4,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[5,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[6,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
      [,12]     [,13]     [,14]     [,15]
[1,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[2,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[3,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[4,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[5,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[6,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"

## End(Not run)

```

c212.BB

Implementation of the Berry and Berry Three-Level Hierarchical Model.

Description

Implementaion of Berry and Berry model (2004), also model 1b from Xia et al (2011).

Usage

```

c212.BB(trial.data, burnin = 20000, iter = 60000, nchains = 3,
theta_algorithm = "MH", sim_type = "SLICE",
global.sim.params = data.frame(type = c("MH", "MH", "MH", "MH",
"SLICE", "SLICE", "SLICE"),
param = c("sigma_MH_alpha", "sigma_MH_beta", "sigma_MH_gamma",
"sigma_MH_theta", "w_alpha", "w_beta", "w_gamma"),
value = c(3, 3, 0.2, 0.2, 1, 1, 1), control = c(0, 0, 0, 0, 6, 6, 6),

```

```

stringsAsFactors = FALSE),
sim.params = NULL,
initial_values = NULL,
hyper_params = list(mu.gamma.0.0 = 0,
tau2.gamma.0.0 = 10, mu.theta.0.0 = 0, tau2.theta.0.0 = 10,
alpha.gamma.0.0 = 3, beta.gamma.0.0 = 1, alpha.theta.0.0 = 3,
beta.theta.0.0 = 1, alpha.gamma = 3,
beta.gamma = 1, alpha.theta = 3, beta.theta = 1,
lambda.alpha = 1.0, lambda.beta = 1.0),
global.pm.weight = 0.5,
pm.weights = NULL,
adapt_params = data.frame(min_w = 0.25, chains = 3, burnin = 20000,
iter = 40000),
adapt_phase=0)

```

Arguments

trial.data	A file or data frame containing the trial data. It must contain must contain the columns <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants).
burnin	The burnin period for the monte-carlo simulation. These are discarded from the returned samples.
iter	The total number of iterations for which the monte-carlo simulation is run. This includes the burnin period. The total number of samples returned is <i>iter - burnin</i>
nchains	The number of independent chains to run.
theta_algorithm	MCMC algorithm used to sample the theta variables. "MH" is the only currently supported stable algorithm.
sim_type	The type of MCMC method to use for simulating from non-standard distributions apart from theta. Allowed values are "MH" and "SLICE" for Metropolis_Hastings and Slice sampling respectively.
global.sim.params	A data frame containing the parameters for the simulation type <i>sim_type</i> . For "MH" the parameter is the variance of the normal distribution used to simulate the next candidate value centred on the current value. For "SLICE" the parameters are the estimated width of the slice and a value limiting the search for the next sample.
sim.params	A dataframe containing simulation parameters which override the global simulation parameters (<i>global.sim.params</i>) for particular model parameters. <i>sim.params</i> must contain the following columns: type: the simulation type ("MH" or "SLICE"); variable: the model parameter for which the simulation parameters are being overridden; B: the body-system (if applicable); AE: the adverse event (if applicable); param: the simulation parameter; value: the overridden value; control: the overridden control value. The function <i>c212.sim.control.params</i> generates a template for <i>sim.params</i> which can be edited by the user.

- `initial_values` The initial values for starting the chains. If NULL (the default) is passed the function generates the initial values for the chains. `initial_values` is a list with the following format:
- ```
list(gamma, theta, mu.gamma, mu.theta, sigma2.gamma,
 sigma2.theta, pi, mu.gamma.0, mu.theta.0,
 tau2.gamma.0, tau2.theta.0, alpha.pi, beta.pi)
```
- The function `c212.gen.initial.values` can be used to generate a template for the list which can be updated by the user if required. The formats of the list elements are as follows:
- `gamma, theta`: dataframe with columns *B*, *AE*, *chain*, *value*  
`mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, pi`: dataframe with columns *B*, *chain*, *value*  
`mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0, alpha.pi, beta.pi`: array of size *chain*.
- `hyper_params` The hyperparameters for the model. The default hyperparameters are those given in Berry and Berry 2004.
- `global.pm.weight`  
 A global weighting for the proposal distribution used to sample theta.
- `pm.weights` Override `global.pm.weight` for specific adverse events.
- `adapt_params` Unused parameter.
- `adapt_phase` Unused parameter.

## Details

The model is fitted by a Gibbs sampler. The details of the complete conditional densities are given in Berry and Berry (2004).

## Value

The output from the simulation including all the sampled values is as follows:

```
list(id, theta_alg, sim_type, chains, nBodySys, maxAEs, nAE, AE, B,
 burnin, iter, mu.gamma.0, mu.theta.0, tau2.gamma.0,
 tau2.theta.0, mu.gamma, mu.theta, sigma2.gamma, sigma2.theta,
 pi, alpha.pi, beta.pi, alpha.pi_acc, beta.pi_acc, gamma, theta,
 gamma_acc, theta_acc, theta_zero_prop, theta_zero_acc)
```

where

*id* - a string identifying the version of the function

*theta\_alg* - an string identifying the algorithm used to sample theta

*sim\_type* - an string identifying the sampling method used for non-standard distributions, either "MH" or "SLICE"

*chains* - the number of chains for which the simulation was run

*nBodySys* - the number of body-systems

*maxAEs* - the maximum number of AEs in a body-system  
*nAE* - an array. The number of AEs in each body-system.  
*AE* - an array of dimension *nBodySys*, *maxAEs*. The Adverse Events.  
*B* - an array. The body-systems.  
*mu.gamma.0* - array of samples of dimension *chains*, *iter* - *burnin*  
*mu.theta.0* - array of samples of dimension *chains*, *iter* - *burnin*  
*tau2.gamma.0* - array of samples of dimension *chains*, *iter* - *burnin*  
*tau2.theta.0* - array of samples of dimension *chains*, *iter* - *burnin*  
*mu.gamma* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*  
*mu.theta* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*  
*sigma2.gamma* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*  
*sigma2.theta* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*  
*pi* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin* *alpha.pi* - array of samples of dimension *chains*, *iter* - *burnin* *beta.pi* - array of samples of dimension *chains*, *iter* - *burnin*  
*alpha.pi\_acc* - the acceptance rate for the alpha.pi samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *maxAEs*  
*beta.pi\_acc* - the acceptance rate for the beta.pi samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *maxAEs*  
*gamma* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*  
*theta* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*  
*gamma\_acc* - the acceptance rate for the gamma samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*  
*theta\_acc* - the acceptance rate for the theta samples. An array of dimension *chains*, *nBodySys*, *maxAEs*  
*theta\_zero\_prop* - the number of zeros proposed in theta sampling. An array of dimension *chains*, *nBodySys*, *maxAEs* *theta\_zero\_acc* - the acceptance rate for zeros for the theta samples. An array of dimension *chains*, *nBodySys*, *maxAEs*

### Note

The function performs the simulation and returns the raw output. No checks for convergence are performed.

### Author(s)

R. Carragher

### References

- S. M. Berry and D. A. Berry (2004). Accounting for multiplicities in assessing drug safety: a three-level hierarchical mixture model. *Biometrics*, 60(2):418-26.
- H. Amy Xia, Haijun Ma, and Bradley P. Carlin (2011). Bayesian hierarchical modelling for detecting safety signals in clinical trials. *Journal of Biopharmaceutical Statistics*, 21(5):1006– 1029.

Scott M. Berry, Bradley P. Carlin, J. Jack Lee, and Peter Müller (2010). Bayesian adaptive methods for clinical trials. CRC Press.

### Examples

```
data(c212.trial.data)
raw = c212.BB(c212.trial.data, burnin = 100, iter = 200)

Not run:
data(c212.trial.data)
raw = c212.BB(c212.trial.data)

raw$B
[1] "Bdy-sys_1" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5" "Bdy-sys_6"
[7] "Bdy-sys_7" "Bdy-sys_8"

mean(raw$theta[2, 1,1,])
[1] 0.1088401

median(raw$theta[2, 1,1,])
[1] 0

End(Not run)
```

---

|                 |                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------|
| c212.BB.interim | <i>A Two or Three-Level Hierarchical Body-system based Model for interim analysis with Point-Mass.</i> |
|-----------------|--------------------------------------------------------------------------------------------------------|

---

### Description

Implementation of a Two or Three-Level Hierarchical Body-system based Model for interim analysis with Point-Mass.

### Usage

```
c212.BB.interim(trial.data, sim_type = "SLICE", burnin = 20000,
 iter = 60000, nchains = 5, theta_algorithm = "MH",
 global.sim.params = NULL,
 sim.params = NULL,
 monitor = NULL,
 initial_values = NULL,
 hier = 3,
 level = 1,
 hyper_params = NULL,
 global.pm.weight = 0.5,
 pm.weights = NULL,
 adapt_phase=1, memory_model = "HIGH")
```

**Arguments**

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>trial.data</code>        | A file or data frame containing the trial data. It must contain must contain the columns <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants).                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <code>burnin</code>            | The burnin period for the monte-carlo simulation. These are discarded from the returned samples.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <code>iter</code>              | The total number of iterations for which the monte-carlo simulation is run. This includes the burnin period. The total number of samples returned is <i>iter - burnin</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <code>nchains</code>           | The number of independent chains to run.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <code>theta_algorithm</code>   | MCMC algorithm used to sample the theta variables. "MH" is the only currently supported stable algorithm.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <code>sim_type</code>          | The type of MCMC method to use for simulating from non-standard distributions apart from theta. Allowed values are "MH" and "SLICE" for Metropolis_Hastings and Slice sampling respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <code>monitor</code>           | A dataframe indicating which sets of variables to monitor. Passing NULL uses the model defaults.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <code>global.sim.params</code> | A data frame containing the parameters for the simulation type <i>sim_type</i> . For "MH" the parameter is the variance of the normal distribution used to simulate the next candidate value centred on the current value. For "SLICE" the parameters are the estimated width of the slice and a value limiting the search for the next sample. Passing NULL uses the model defaults.                                                                                                                                                                                                                                                                                                                                                                  |
| <code>sim.params</code>        | A dataframe containing simulation parameters which override the global simulation parameters ( <i>global.sim.params</i> ) for particular model parameters. <i>sim.params</i> must contain the following columns: type: the simulation type ("MH" or "SLICE"); variable: the model parameter for which the simulation parameters are being overridden; B: the body-system (if applicable); AE: the adverse event (if applicable); param: the simulation parameter; value: the overridden value; control: the overridden control value.<br><br>The function <i>c212.sim.control.params</i> generates a template for <i>sim.params</i> which can be edited by the user.                                                                                   |
| <code>initial_values</code>    | The initial values for starting the chains. If NULL (the default) is passed the function generates the initial values for the chains. <i>initial_values</i> is a list with the following format:<br><br><pre>list(gamma, theta, mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, pi, mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0, alpha.pi, beta.pi)</pre><br>The function <i>c212.gen.initial.values</i> can be used to generate a template for the list which can be updated by the user if required. The formats of the list elements are as follows:<br><i>gamma, theta</i> : dataframe with columns <i>B, AE, chain, value</i><br><i>mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, pi</i> : dataframe with columns <i>B, chain, value</i> |



|                         |                                                                                                                                                                                                                                               |
|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                         | <i>mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0, alpha.pi, beta.pi</i> : array of size <i>chain</i> .                                                                                                                                   |
| <i>hier</i>             | Model using a two or three level hierarchy. 2 - two-level hierarchy, 3 - three level hierarchy.                                                                                                                                               |
| <i>level</i>            | The level of longitudinal dependency between the intervals. Allowed values are 0, 1, 2 for a three-level hierarchy and 0, 1 for a two-level hierarchy. 0 - independent intervals, 1 - common interval body-system means, 2 - weak dependency. |
| <i>hyper_params</i>     | The hyperparameters for the model. The default hyperparameters are those given in Berry and Berry 2004. Passing NULL uses the model defaults.                                                                                                 |
| <i>global.pm.weight</i> | A global weighting for the proposal distribution used to sample theta.                                                                                                                                                                        |
| <i>pm.weights</i>       | Override <i>global.pm.weight</i> for specific adverse events.                                                                                                                                                                                 |
| <i>adapt_phase</i>      | Unused parameter.                                                                                                                                                                                                                             |
| <i>memory_model</i>     | Allowed values are "HIGH" and "LOW". "HIGH" means use as much memory as possible. "LOW" means use the minimum amount of memory.                                                                                                               |

## Details

The model is fitted by a Gibbs sampler. The details of the complete conditional densities are given in Berry and Berry (2004).

## Value

The output from the simulation including all the sampled values for the three-level hierarchy is as follows:

```
list(id, sim_type, chains, nIntervals, Intervals, nBodySys,
maxBs, maxAEs, nAE, AE, B, burnin,
iter, monitor, mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0,
gamma, theta, mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, pi,
alpha.pi, beta.pi,
alpha.pi_acc, beta.pi_acc, gamma_acc, theta_acc)
```

The output from the simulation including all the sampled values for the two-level hierarchy is as follows:

```
list(id, sim_type, chains, nIntervals, Intervals, nBodySys,
maxBs, maxAEs, nAE, AE, B, burnin,
iter, monitor,
gamma, theta,
mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, pi,
gamma_acc, theta_acc)
```

where

*id* - a string identifying the version of the function

*sim\_type* - an string identifying the sampling method used for non-standard distributions, either "MH" or "SLICE"

*chains* - the number of chains for which the simulation was run  
*nIntervals* - the number of intervals in the simulation  
*Intervals* - an array. The intervals.  
*nBodySys* - the number of body-systems  
*maxBs* - the maximum number of body-systems in an interval  
*maxAEs* - the maximum number of AEs in a body-system  
*nAE* - an array. The number of AEs in each body-system.  
*AE* - an array of dimension *nBodySys*, *maxAEs*. The Adverse Events.  
*B* - an array. The body-systems.  
*burnin* - burnin used for the simulation.  
*iter* - the total number of iterations in the simulation.  
*monitor* - the variables being monitored. A dataframe.  
*mu.gamma.0* - array of samples of dimension *chains*, *iter - burnin*  
*mu.theta.0* - array of samples of dimension *chains*, *iter - burnin*  
*tau2.gamma.0* - array of samples of dimension *chains*, *iter - burnin*  
*tau2.theta.0* - array of samples of dimension *chains*, *iter - burnin*  
*mu.gamma* - array of samples of dimension *chains*, *nBodySys iter - burnin*  
*mu.theta* - array of samples of dimension *chains*, *nBodySys iter - burnin*  
*sigma.gamma* - array of samples of dimension *chains*, *nBodySys iter - burnin*  
*sigma.theta* - array of samples of dimension *chains*, *nBodySys iter - burnin*  
*pi* - array of samples of dimension *chains*, *nBodySys iter - burnin* *alpha.pi* - array of samples of dimension *chains*, *iter - burnin* *beta.pi* - array of samples of dimension *chains*, *iter - burnin*  
*alpha.pi\_acc* - the acceptance rate for the alpha.pi samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *maxAEs*  
*beta.pi\_acc* - the acceptance rate for the beta.pi samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *maxAEs*  
*gamma* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter - burnin*  
*theta* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter - burnin*  
*gamma\_acc* - the acceptance rate for the gamma samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*  
*theta\_acc* - the acceptance rate for the theta samples. An array of dimension *chains*, *nBodySys*, *maxAEs*

### Note

The function performs the simulation and returns the raw output. No checks for convergence are performed.

### Author(s)

R. Carragher

**Examples**

```

data(c212.trial.interval.data1)
raw = c212.BB.interim(c212.trial.interval.data1, level = 1, burnin = 100, iter = 200)

Not run:
data(c212.trial.interval.data1)
raw = c212.BB.interim(c212.trial.interval.data1, level = 1)

raw$B
 [,1] [,2] [,3] [,4] [,5]
[1,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[2,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[3,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[4,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[5,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[6,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
 [,6] [,7] [,8] [,9] [,10] [,11]
[1,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[2,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[3,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[4,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[5,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[6,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
 [,12] [,13] [,14] [,15]
[1,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[2,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[3,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[4,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[5,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[6,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"

End(Not run)

```

c212.BH

---

*Implementation of Benjamini-Hochberg procedure for False Discovery Rate control*

---

**Description**

Implementaion of Benjamini-Hochberg procedure for False Discovery Rate control. The hypotheses' data can be contained in a file or data frame.

**Usage**

```
c212.BH(trial.data, alpha = 0.05)
```

**Arguments**

|            |                                                                                                                                                                           |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data | File or data frame containing the p-values for the hypotheses being tested. The data must include a column called <i>p</i> which contains the p-values of the hypotheses. |
| alpha      | The level for FDR control. E.g. 0.05.                                                                                                                                     |

**Value**

The subset of hypotheses in *file* or *trial.data* deemed significant by the Benjamini-Hochberg procedure.

**Note**

No check is made for duplicate rows in the input file or data frame.

**Author(s)**

R. Carragher<raymond.carragher@strath.ac.uk>

**References**

Benjamini, Yoav and Hochberg, Yosef, (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, 57(1):289-300.

**Examples**

```
trial.data <- data.frame(B = c(1, 2, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 4, 4),
 j = c(1, 1, 2, 3, 4, 1, 2, 3, 4, 5, 6, 7, 1, 2, 3, 4, 5),
 AE = c("AE1", "AE2", "AE3", "AE4", "AE5", "AE6", "AE7", "AE8", "AE9", "AE10", "AE11",
 "AE12", "AE13", "AE14", "AE15", "AE16", "AE17"),
 p = c(0.135005, 0.010000, 0.001000, 0.005000, 0.153501, 0.020000, 0.0013, 0.0023,
 0.011, 0.023000, 0.016, 0.0109, 0.559111, 0.751986, 0.308339, 0.837154, 0.325882))
```

```
c212.BH(trial.data, 0.05)
```

```
Not run:
```

```
 B j AE p
1 2 2 AE3 0.0010
2 3 2 AE7 0.0013
3 3 3 AE8 0.0023
4 2 3 AE4 0.0050
5 2 1 AE2 0.0100
6 3 7 AE12 0.0109
7 3 4 AE9 0.0110
8 3 6 AE11 0.0160
9 3 1 AE6 0.0200
10 3 5 AE10 0.0230
```

```
End(Not run)
```

---

c212.BH.adjust.pvals *Benjamini-Hochberg procedure adjusted p-values*

---

### Description

Benjamini-Hochberg procedure adjusted p-values.

### Usage

```
c212.BH.adjust.pvals(trial.data)
```

### Arguments

|                         |                                                                                                                                                                           |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>trial.data</code> | File or data frame containing the p-values for the hypotheses being tested. The data must include a column called <i>p</i> which contains the p-values of the hypotheses. |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### Value

Returns the original data frame, ordered by *p*, with an additional column *p\_adj*.

### Note

The adjusted p values may be directly compared to a value *alpha* to determine whether to declare a hypothesis significant under the Benjamini-Hochberg procedure at level *alpha*.

### Note

No check is made for duplicate rows in the input file or data frame.

### Author(s)

R. Carragher<raymond.carragher@strath.ac.uk>

### References

D. V. Mehrotra and J. F. Heyse (2004). Use of the false discovery rate for evaluating clinical safety data. *Stat Methods Med Res*, 13(3):227–38, 2004.

**Examples**

```

trial.data <- data.frame(B = c(1, 2, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 4, 4),
 j = c(1, 1, 2, 3, 4, 1, 2, 3, 4, 5, 6, 7, 1, 2, 3, 4, 5),
 AE = c("AE1", "AE2", "AE3", "AE4", "AE5", "AE6", "AE7", "AE8", "AE9", "AE10", "AE11",
 "AE12", "AE13", "AE14", "AE15", "AE16", "AE17"),
 p = c(0.135005, 0.010000, 0.001000, 0.005000, 0.153501, 0.020000, 0.0013, 0.0023,
 0.011, 0.023000, 0.016, 0.0109, 0.559111, 0.751986, 0.308339, 0.837154, 0.325882))

```

```
adj <- c212.BH.adjust.pvals(trial.data)
```

```
Not run:
```

```
adj:
```

```
====
```

|    | B | j | AE   | p        | p_adj      |
|----|---|---|------|----------|------------|
| 1  | 2 | 2 | AE3  | 0.001000 | 0.01105000 |
| 2  | 3 | 2 | AE7  | 0.001300 | 0.01105000 |
| 3  | 3 | 3 | AE8  | 0.002300 | 0.01303333 |
| 4  | 2 | 3 | AE4  | 0.005000 | 0.02125000 |
| 5  | 2 | 1 | AE2  | 0.010000 | 0.02671429 |
| 6  | 3 | 7 | AE12 | 0.010900 | 0.02671429 |
| 7  | 3 | 4 | AE9  | 0.011000 | 0.02671429 |
| 8  | 3 | 6 | AE11 | 0.016000 | 0.03400000 |
| 9  | 3 | 1 | AE6  | 0.020000 | 0.03777778 |
| 10 | 3 | 5 | AE10 | 0.023000 | 0.03910000 |
| 11 | 1 | 1 | AE1  | 0.135005 | 0.20864409 |
| 12 | 2 | 4 | AE5  | 0.153501 | 0.21745975 |
| 13 | 4 | 3 | AE15 | 0.308339 | 0.39571386 |
| 14 | 4 | 5 | AE17 | 0.325882 | 0.39571386 |
| 15 | 4 | 1 | AE13 | 0.559111 | 0.63365913 |
| 16 | 4 | 2 | AE14 | 0.751986 | 0.79898513 |
| 17 | 4 | 4 | AE16 | 0.837154 | 0.83715400 |

```
End(Not run)
```

```
adj[adj$p_adj <= 0.05,]
```

```
Not run:
```

|    | B | j | AE   | p      | p_adj      |
|----|---|---|------|--------|------------|
| 1  | 2 | 2 | AE3  | 0.0010 | 0.01105000 |
| 2  | 3 | 2 | AE7  | 0.0013 | 0.01105000 |
| 3  | 3 | 3 | AE8  | 0.0023 | 0.01303333 |
| 4  | 2 | 3 | AE4  | 0.0050 | 0.02125000 |
| 5  | 2 | 1 | AE2  | 0.0100 | 0.02671429 |
| 6  | 3 | 7 | AE12 | 0.0109 | 0.02671429 |
| 7  | 3 | 4 | AE9  | 0.0110 | 0.02671429 |
| 8  | 3 | 6 | AE11 | 0.0160 | 0.03400000 |
| 9  | 3 | 1 | AE6  | 0.0200 | 0.03777778 |
| 10 | 3 | 5 | AE10 | 0.0230 | 0.03910000 |

```
End(Not run)
```

---

`c212.bin.test`*Plot Raw Adverse Event Incidence Data*

---

**Description**

Test the hypothesis that the proportions in two groups are the same. adverse event.

**Usage**

```
c212.bin.test(trial.data, alternative = "two.sided", correct = TRUE)
```

**Arguments**

|                          |                                                                                                                                                                                                                                                                         |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>trial.data</code>  | A file or data frame containing the trial data. The data frame must contain the columns <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants). |
| <code>alternative</code> | Alternative hypothesis may be "two.sided", "greater" or "less". The default is "two.sided".                                                                                                                                                                             |
| <code>correct</code>     | Apply a continuity correction.                                                                                                                                                                                                                                          |

**Details**

Test the hypothesis that the proportions in two groups are the same.

**Value**

Dataframe containing the results of the test. A copy of the input dataframe with an additional column *p* containing the p-value from the test.

**Note**

Wrapper for the R function 'prop.test' in package 'stats'.

**Author(s)**

R. Carragher

### Examples

```
data(c212.trial.data)
pr = c212.bin.test(c212.trial.data)
head(pr)

Not run:
 B j AE p
1 Bdy-sys_1 1 Adv-Ev_1 2.893605e-01
2 Bdy-sys_2 1 Adv-Ev_2 5.711463e-03
3 Bdy-sys_2 2 Adv-Ev_3 1.655715e-02
4 Bdy-sys_2 3 Adv-Ev_4 6.497695e-01
5 Bdy-sys_2 4 Adv-Ev_5 7.433433e-01
6 Bdy-sys_3 1 Adv-Ev_6 8.419469e-08

End(Not run)
```

---

c212.BONF

*Implementation of Bonferroni correction for error control*

---

### Description

The Bonferroni correction controls the Familywise Error Rate.

### Usage

```
c212.BONF(trial.data, alpha = 0.05)
```

### Arguments

|            |                                                                                                                                                                           |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data | File or data frame containing the p-values for the hypotheses being tested. The data must include a column called <i>p</i> which contains the p-values of the hypotheses. |
| alpha      | The value for error control, e.g. 0.05.                                                                                                                                   |

### Value

The subset of hypotheses in *file* or *trial.data* deemed significant.

### Note

No check is made for duplicate rows in the input file or data frame.

### Author(s)

R. Carragher



## References

Matthews, John N. S. (2006) Introduction to Randomized Controlled Clinical Trials, Second Edition. Chapman & Hall/CRC Texts in Statistical Science.

## Examples

```
trial.data <- data.frame(B = c(1, 2, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 4, 4),
 j = c(1, 1, 2, 3, 4, 1, 2, 3, 4, 5, 6, 7, 1, 2, 3, 4, 5),
 AE = c("AE1", "AE2", "AE3", "AE4", "AE5", "AE6", "AE7", "AE8", "AE9", "AE10", "AE11",
 "AE12", "AE13", "AE14", "AE15", "AE16", "AE17"),
 p = c(0.135005, 0.010000, 0.001000, 0.005000, 0.153501, 0.020000, 0.0013, 0.0023, 0.011,
 0.023000, 0.016, 0.0109, 0.559111, 0.751986, 0.308339, 0.837154, 0.325882))
```

```
c212.BONF(trial.data, 0.05)
```

```
Not run:
```

```
 B j AE p
1 2 2 AE3 0.0010
2 3 2 AE7 0.0013
3 3 3 AE8 0.0023
```

```
End(Not run)
```

---

c212.convergence.diag *Convergence Diagnostics of the Simulation*

---

## Description

The function applies either Gelman-Rubin or the Geweke diagnostic to the raw output of model simulation (e.g. c212.BB). It returns the convergence diagnostics and, if applicable, the acceptance rates for the sampling distributions.

## Usage

```
c212.convergence.diag(raw, debug_diagnostic = FALSE)
```

## Arguments

raw                    The output from a model simulation.

debug\_diagnostic      Unused parameter.

## Details

parameter is time consuming. This function applies one of two convergence diagnostics to the raw output of a model simulation in order to allow convergence to be assessed. The two diagnostics are:

- i) Gelman-Rubin diagnostic - used when there is more than one chain. A value close to 1 is consistent with an MCMC simulation which has converged. The 'coda' diagnostic returns a point estimate and upper confidence limits.
- ii) Geweke diagnostic - used when there is a single chain. A Z-score which is consistent with a standard normal distribution is expected from an MCMC simulation which has converged.

The raw sample data is converted to 'coda' format (mcmc objects) and the 'coda' methods `gelman.diag` and `geweke.diag` are used to perform the checks.

## Value

Returns a list of the diagnostics for each sampled variable. Each individual element of the list is a data.frame containing at least the columns *type*, which is the type of diagnostic ('Gelman-Rubin' or 'Geweke'), *stat*, which is the value of the diagnostic, and *upper\_ci* which is the upper confidence interval for the Gelman-Rubin diagnostic. For the Geweke diagnostic *upper\_ci* contains the value NA. Depending on the simulation performed the return from `c212.convergence.diag` will contain different variables. The return for a simulation from `c212.1a` is as follows:

```
list(sim_type, gamma.conv.diag, theta.conv.diag, mu.gamma.conv.diag,
 mu.theta.conv.diag, sigma2.gamma.conv.diag,
 sigma2.theta.conv.diag, mu.gamma.0.conv.diag,
 mu.theta.0.conv.diag, tau2.gamma.0.conv.diag,
 tau2.theta.0.conv.diag)
```

Additional columns which may be used to identify the individual samples are *B*, the body-system, and *AE*, the Adverse Event and *interval*.

## Author(s)

R. Carragher

## Examples

```
data(c212.trial.data)
raw = c212.BB(c212.trial.data, burnin = 100, iter = 200)
conv = c212.convergence.diag(raw)

Not run:
data(c212.trial.data)
raw = c212.BB(c212.trial.data)
conv = c212.convergence.diag(raw)

End(Not run)
```

c212.DFDR

*Implementation of the Double False Discovery Rate for controlling the False Discovery Rate.*

## Description

The Double False Discovery Rate is designed to take advantage of possible groupings which may exist within sets of hypotheses. It applies the BH-procedure twice. Once at the group level, to identify sets of hypotheses which may contain significant hypotheses. It then groups these hypotheses together to form a single family and applies the BH-procedure again to declare hypotheses significant.

## Usage

```
c212.DFDR(trial.data, alpha = 0.05)
```

## Arguments

|            |                                                                                                                                                                                                                    |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data | File or data frame containing the p-values for the hypotheses being tested. The data must contain the following columns: <i>B</i> : the index or name of the groupings; <i>p</i> : the p-values of the hypotheses. |
| alpha      | The level for FDR control. E.g. 0.05.                                                                                                                                                                              |

## Value

The subset of hypotheses in *file* or *trial.data* deemed significant by the Double False Discovery Rate process.

## Author(s)

R. Carragher

## References

Mehrotra, D. V. and Adewale, A. J. (2012). Flagging clinical adverse experiences: reducing false discoveries without materially compromising power for detecting true signals. *Stat Med*, 31(18):1918-30.

## Examples

```
trial.data <- data.frame(B = c(1, 2, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 4, 4),
 AE = c("AE1", "AE2", "AE3", "AE4", "AE5", "AE6", "AE7", "AE8", "AE9", "AE10", "AE11",
 "AE12", "AE13", "AE14", "AE15", "AE16", "AE17"),
 p = c(0.135005, 0.010000, 0.001000, 0.005000, 0.153501, 0.020000, 0.0013, 0.0023,
 0.011, 0.023000, 0.016, 0.0109, 0.559111, 0.751986, 0.308339, 0.837154, 0.325882))
```

```
c212.DFDR(trial.data, 0.05)
```

```
Not run:
 B j AE p
1 2 2 AE3 0.0010
2 3 2 AE7 0.0013
3 3 3 AE8 0.0023
4 2 3 AE4 0.0050
5 2 1 AE2 0.0100
6 3 7 AE12 0.0109
7 3 4 AE9 0.0110
8 3 6 AE11 0.0160
9 3 1 AE6 0.0200
10 3 5 AE10 0.0230

End(Not run)
```

---

c212.err.cntnl

*Implementaion of Group Bonferroni-Hochberg procedure for control of the False Discovery Rate*

---

## Description

Common interface to the error controlling methods: Unadjutsed hypothesis testing (NOADJ), Bonferroni correction (BONF), Benjamini-Hochberg procedure (BH), Group Benjamini-Hochberg (GBH), Double False Discover Rate (DFDR), subset Benjamini-Hochberg (ssBH).

## Usage

```
c212.err.cntnl(trial.data, alpha = 0.05, method = "NOADJ",...)
```

## Arguments

|            |                                                                                                                                                                                                                                                     |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data | File or data frame containing the p-values for the hypotheses being tested. The data must contain the following columns: <i>B</i> : the index or name of the groupings; <i>p</i> : the p-values of the hypotheses.                                  |
| alpha      | The level for error control. E.g. 0.05.                                                                                                                                                                                                             |
| method     | The error control procedure to be applied: "NOAD" - unadjusted testing, "BONF" - Bonferroni correction "BH" - Benjamini-Hochberg procedure "GBH" - Group Benjamini-Hochberg "DFDR" - Double False Discover Rate "ssBH" - subset Benjamini-Hochberg. |
| ...        | Additional optional parameter for the GBH method: $\pi_0$ .                                                                                                                                                                                         |

## Value

The subset of hypotheses in *file* or *trial.data* deemed significant by the Group Benjamini-Hochberg process.

**Author(s)**

R. Carragher

**Examples**

```

trial.data <- data.frame(B = c(1, 2, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 4, 4),
j = c(1, 1, 2, 3, 4, 1, 2, 3, 4, 5, 6, 7, 1, 2, 3, 4, 5),
AE = c("AE1", "AE2", "AE3", "AE4", "AE5", "AE6", "AE7", "AE8", "AE9", "AE10", "AE11",
"AE12", "AE13", "AE14", "AE15", "AE16", "AE17"),
p = c(0.135005, 0.010000, 0.001000, 0.005000, 0.153501, 0.020000, 0.0013, 0.0023,
0.011, 0.023000, 0.016, 0.0109, 0.559111, 0.751986, 0.308339, 0.837154, 0.325882))

```

```

c212.err.cntrl(trial.data = trial.data, alpha = 0.05, method = "GBH")

```

```

Not run:

```

```

 B j AE p p_weighted
1 3 1 AE6 0.020000 0.0000000000
2 3 2 AE7 0.001300 0.0000000000
3 3 3 AE8 0.002300 0.0000000000
4 3 4 AE9 0.011000 0.0000000000
5 3 5 AE10 0.023000 0.0000000000
6 3 6 AE11 0.016000 0.0000000000
7 3 7 AE12 0.010900 0.0000000000
8 2 2 AE3 0.001000 0.0003333333
9 2 3 AE4 0.005000 0.0016666667
10 2 1 AE2 0.010000 0.0033333333
11 2 4 AE5 0.153501 0.0511670000

```

```

End(Not run)

```

---

c212.FDR.data

*Fisher Test p-values for End of Trial Data Clinical Data*


---

**Description**

This data set the p-values for a comparison between adverse events on each arm of a clinical trial.

**Usage**

```

data(c212.FDR.data)

```

**Format**

A dataframe with columns *B* - body-system, *AE* - adverse event, *p* - p-value for two-sided Fisher exact test. The dataframe contains 45 observations.

---

c212.fisher.test      *Fisher Exact Test*

---

### Description

Perform a Fisher exact test on clinical trial data.

### Usage

```
c212.fisher.test(trial.data, alternative = "two.sided")
```

### Arguments

|             |                                                                                                                                                                                                                                                                         |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data  | A file or data frame containing the trial data. The data frame must contain the columns <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants). |
| alternative | Alternative hypothesis may be "two.sided", "greater" or "less". The default is "two.sided".                                                                                                                                                                             |

### Details

Perform a Fisher exact test on clinical trial data.

### Value

Dataframe containing the results of the test. A copy of the input dataframe with an additional column *p* containing the p-value from the test.

### Note

Wrapper for the R function 'fisher.test' in package 'stats'.

### Author(s)

R. Carragher

### Examples

```
data(c212.trial.data)
f = c212.fisher.test(c212.trial.data)

Not run:
data(c212.trial.data)
f = c212.fisher.test(c212.trial.data)
head(f)
 B j AE p
1 Bdy-sys_1 1 Adv-Ev_1 2.892876e-01
2 Bdy-sys_2 1 Adv-Ev_2 5.333164e-03
3 Bdy-sys_2 2 Adv-Ev_3 1.601311e-02
```

```

4 Bdy-sys_2 3 Adv-Ev_4 6.502108e-01
5 Bdy-sys_2 4 Adv-Ev_5 7.437946e-01
6 Bdy-sys_3 1 Adv-Ev_6 3.746249e-08

```

```
End(Not run)
```

---

|          |                                                                                                     |
|----------|-----------------------------------------------------------------------------------------------------|
| c212.GBH | <i>Implementaion of Group Bonferroni-Hochberg procedure for control of the False Discovery Rate</i> |
|----------|-----------------------------------------------------------------------------------------------------|

---

### Description

The Group Benjamini-Hochberg procedure for control of the False Discovery Rate is designed to take advantage of possible groupings which may exist within sets of hypotheses. The procedure estimates the number of true null hypotheses in each grouping and uses this to weight the p-values which are then compared to a weighted level for control. The procedure asymptotically controls the False Discovery Rate at the required level.

### Usage

```
c212.GBH(trial.data, pi0 = "TST", alpha)
```

### Arguments

|            |                                                                                                                                                                                                                    |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data | File or data frame containing the p-values for the hypotheses being tested. The data must contain the following columns: <i>B</i> : the index or name of the groupings; <i>p</i> : the p-values of the hypotheses. |
| pi0        | The estimator to use for the estimation of the number of true null hypotheses in each group. Valid values are "TST" and "LSL".                                                                                     |
| alpha      | The level for FDR control. E.g. 0.05.                                                                                                                                                                              |

### Value

The subset of hypotheses in *file* or *trial.data* deemed significant by the Group Benjamini-Hochberg process.

### Note

The estimator "TST" is the two-stage estimator of Benjamini, Krieger, and Yekutieli. The estimator "LSL" is the least-slope estimator of Benjamini and Hochberg.

### Author(s)

R. Carragher

## References

- Hu, J. X. and Zhao, H. and Zhou, H. H. (2010). False Discovery Rate Control With Groups. *J Am Stat Assoc*, 105(491):1215-1227.
- Y. Benjamini, A. M. Krieger, and D. Yekutieli (2006). Adaptive linear step-up procedures that control the false discovery rate. *Biometrika*, 93(3):491–507.
- Benjamini Y, Hochberg Y. (2000). On the Adaptive Control of the False Discovery Rate in Multiple Testing With Independent Statistics. *Journal of Educational and Behavioral Statistics*, 25(1):60–83.

## Examples

```

trial.data <- data.frame(B = c(1, 2, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 4, 4),
 j = c(1, 1, 2, 3, 4, 1, 2, 3, 4, 5, 6, 7, 1, 2, 3, 4, 5),
 AE = c("AE1", "AE2", "AE3", "AE4", "AE5", "AE6", "AE7", "AE8", "AE9", "AE10", "AE11",
 "AE12", "AE13", "AE14", "AE15", "AE16", "AE17"),
 p = c(0.135005, 0.010000, 0.001000, 0.005000, 0.153501, 0.020000, 0.0013, 0.0023,
 0.011, 0.023000, 0.016, 0.0109, 0.559111, 0.751986, 0.308339, 0.837154, 0.325882))

c212.GBH(trial.data, pi0 = "TST", 0.05)

Not run:
 B j AE p p_weighted
1 3 1 AE6 0.020000 0.0000000000
2 3 2 AE7 0.001300 0.0000000000
3 3 3 AE8 0.002300 0.0000000000
4 3 4 AE9 0.011000 0.0000000000
5 3 5 AE10 0.023000 0.0000000000
6 3 6 AE11 0.016000 0.0000000000
7 3 7 AE12 0.010900 0.0000000000
8 2 2 AE3 0.001000 0.0003333333
9 2 3 AE4 0.005000 0.0016666667
10 2 1 AE2 0.010000 0.0033333333
11 2 4 AE5 0.153501 0.0511670000

End(Not run)

```

---

```
c212.gen.initial.values
```

*Generate a template simulation initial values.*

---

## Description

This function generates a template for the initial values to be used to start the simulation. They can be updated by the caller and passed to the simulation function.

## Usage

```

c212.gen.initial.values(trial.data, nchains = 3,
 model = "1a", hier = 3, level = 0)

```



**Arguments**

|            |                                                                                              |
|------------|----------------------------------------------------------------------------------------------|
| trial.data | A file or data frame containing the trial data, either for end of trial or interim analysis. |
| nchains    | The number of chains in the simulation.                                                      |
| model      | The model type: "BB" for point-mass models, "1a" for non-point-mass models.                  |
| hier       | Allowed values are 2, 3 indicating two or three level hierarchies.                           |
| level      | The dependency level in the model: 0, 1, 2.                                                  |

**Value**

A dataframe containing the template of initial values.

**Author(s)**

R. Carragher

**Examples**

```
data(c212.trial.data)
init.vals <- c212.gen.initial.values(c212.trial.data)
print(init.vals$mu.gamma.0)
Not run:
data(c212.trial.data)
init.vals <- c212.gen.initial.values(c212.trial.data)
print(init.vals$mu.gamma.0)

End(Not run)
```

---

c212.global.sim.params

*Generate a template for the individual model parameter simulation control parameters.*

---

**Description**

This function generates the default global simulation parameters used by the model simulation functions (e.g. c212.BB).

**Usage**

```
c212.global.sim.params(trial.data, model = "BB", hier = 3)
```

**Arguments**

|            |                                                                                                        |
|------------|--------------------------------------------------------------------------------------------------------|
| trial.data | A file or data frame containing the trial data, either for end of trial or interim analysis.           |
| model      | Allowed values are "BB" and "1a" for point-mass and non-point-mass models respectively.                |
| hier       | Generate parameters for a two level or three level hierarchy. Allowed values are 2 and 3 respectively. |

**Value**

A dataframe containing the global simulation parameters.

**Author(s)**

R. Carragher

**Examples**

```
data(c212.trial.data)
global.sim.prams <- c212.global.sim.params(c212.trial.data)
Not run:
data(c212.trial.data)
global.sim.prams <- c212.global.sim.params(c212.trial.data)

End(Not run)
```

---

|                   |                                                                                              |
|-------------------|----------------------------------------------------------------------------------------------|
| c212.hyper.params | <i>Generate a template for the individual model parameter simulation control parameters.</i> |
|-------------------|----------------------------------------------------------------------------------------------|

---

**Description**

This function generates the default model hyper-parameters used by the model simulation functions (e.g. c212.BB).

**Usage**

```
c212.hyper.params(trial.data, model = "BB", hier = 3)
```

**Arguments**

|            |                                                                                                        |
|------------|--------------------------------------------------------------------------------------------------------|
| trial.data | A file or data frame containing the trial data, either for end of trial or interim analysis.           |
| model      | Allowed values are "BB" and "1a" for point-mass and non-point-mass models respectively.                |
| hier       | Generate parameters for a two level or three level hierarchy. Allowed values are 2 and 3 respectively. |

**Value**

A list containing the model hyper-parameters.

**Author(s)**

R. Carragher

**Examples**

```
data(c212.trial.data)
h.p <- c212.hyper.params(c212.trial.data)
Not run:
data(c212.trial.data)
h.p <- c212.hyper.params(c212.trial.data)
print(h.p)

End(Not run)
```

---

c212.interim.1a.hier2 *A Two-Level Hierarchical Body-system based Model for interim analysis without Point-Mass.*

---

**Description**

Implementation of a Two-Level Hierarchical Body-system based Model for interim analysis without Point-Mass.

**Usage**

```
c212.interim.1a.hier2(trial.data, sim_type = "SLICE", burnin = 10000,
 iter = 40000, nchains = 3,
 global.sim.params = data.frame(type = c("MH", "SLICE"),
 param = c("sigma_MH", "w"), value = c(0.2,1), control = c(0,6),
 stringsAsFactors = FALSE),
 sim.params = NULL,
 monitor = data.frame(variable = c("theta", "gamma", "mu.gamma",
 "mu.theta", "sigma2.theta", "sigma2.gamma"),
 monitor = c(1, 1, 1, 1, 1, 1),
 stringsAsFactors = FALSE),
 initial_values = NULL,
 level = 1,
 hyper_params = list(mu.gamma.0 = 0, tau2.gamma.0 = 10, mu.theta.0 = 0,
 tau2.theta.0 = 10, alpha.gamma = 3, beta.gamma = 1,
 alpha.theta = 3, beta.theta = 1),
 memory_model = "HIGH")
```

**Arguments**

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>trial.data</code>        | A file or data frame containing the trial data. It must contain must contain the columns <i>I_index</i> (interval index), <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants in the trial arm).                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <code>sim_type</code>          | The type of MCMC method to use for simulating from non-standard distributions. Allowed values are "MH" and "SLICE" for Metropolis_Hastings and Slice sampling respectively.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <code>burnin</code>            | The burnin period for the monte-carlo simulation. These are discarded from the returned samples.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <code>iter</code>              | The total number of iterations for which the monte-carlo simulation is run. This includes the burnin period. The total number of samples returned is <i>iter - burnin</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <code>nchains</code>           | The number of independent chains to run.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <code>global.sim.params</code> | A data frame containing the parameters for the simulation type <i>sim_type</i> . For "MH" the parameter is the variance of the normal distribution used to simulate the next candidate value centred on the current value. For "SLICE" the parameters are the estimated width of the slice and a value limiting the search for the next sample.                                                                                                                                                                                                                                                                                                                                                                                            |
| <code>sim.params</code>        | A dataframe containing simulation parameters which override the global simulation parameters ( <i>global.sim.params</i> ) for particular model parameters. <i>sim.params</i> must contain the following columns: type: the simulation type ("MH" or "SLICE"); variable: the model parameter for which the simulation parameters are being overridden; B: the body-system (if applicable); AE: the adverse event (if applicable); param: the simulation parameter; value: the overridden value; control: the overridden control value.<br><br>The function <i>c212.sim.control.params</i> generates a template for <i>sim.params</i> which can be edited by the user.                                                                       |
| <code>monitor</code>           | A dataframe indicating which sets of variables to monitor.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <code>initial_values</code>    | The initial values for starting the chains. If NULL (the default) is passed the function generates the initial values for the chains. <i>initial_values</i> is a list with the following format:<br><br><pre>list(gamma, theta, mu.gamma, mu.theta, sigma2.gamma, sigma2.theta)</pre><br>where each element of the list is either a dataframe or array. The function <i>c212.gen.initial.values</i> can be used to generate a template for the list which can be updated by the user if required. The formats of the list elements are as follows:<br><br><i>gamma, theta</i> : dataframe with columns <i>B, AE, chain, value</i><br><i>mu.gamma, mu.theta, sigma2.gamma, sigma2.theta</i> : dataframe with columns <i>B, chain, value</i> |
| <code>level</code>             | The level of longitudinal dependency between the intervals. 0 - independent intervals, 1 - common interval body-system means.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

|              |                                                                                                                                 |
|--------------|---------------------------------------------------------------------------------------------------------------------------------|
| hyper_params | The hyperparameters for the model. The default hyperparameters are those given in Berry and Berry 2004.                         |
| memory_model | Allowed values are "HIGH" and "LOW". "HIGH" means use as much memory as possible. "LOW" means use the minimum amount of memory. |

## Details

The model is fitted by a Gibbs sampler. The posterior distributions for *gamma* and *theta* are sampled with either a Metropolis-Hastings step or a slice sampler.

## Value

The output from the simulation including all the sampled values is as follows:

```
list(id, sim_type, chains, nIntervals, Intervals, nBodySys, maxBs,
maxAEs, nAE, AE, B, burnin, iter, monitor,
mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, gamma,
theta, gamma_acc, theta_acc)
```

where

*id* - a string identifying the version of the function

*sim\_type* - an string identifying the sampling method used for non-standard distributions, either "MH" or "SLICE"

*chains* - the number of chains for which the simulation was run.

*nIntervals* - the number of intervals in the simulation

*Intervals* - an array. The intervals.

*nBodySys* - the number of body-systems

*maxBs* - the maximum number of body-systems in an interval

*maxAEs* - the maximum number of AEs in a body-system

*nAE* - an array. The number of AEs in each body-system.

*AE* - an array of dimension *nBodySys*, *maxAEs*. The Adverse Events.

*B* - an array. The body-systems.

*burnin* - burnin used for the simulation.

*iter* - the total number of iterations in the simulation.

*monitor* - the variables being monitored. A dataframe.

*mu.gamma* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

*mu.theta* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

*sigma2.gamma* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

*sigma2.theta* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

*gamma* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*

*theta* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*

*gamma\_acc* - the acceptance rate for the gamma samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

*theta\_acc* - the acceptance rate for the theta samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

### Note

The function performs the simulation and returns the raw output. No checks for convergence are performed.

### Author(s)

R. Carragher

### Examples

```
data(c212.trial.interval.data1)
raw = c212.interim.1a.hier2(c212.trial.interval.data1, level = 1, burnin = 100, iter = 200)
Not run:
data(c212.trial.interval.data1)
raw = c212.interim.1a.hier2(c212.trial.interval.data1, level = 1)

raw$B
 [,1] [,2] [,3] [,4] [,5]
[1,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[2,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[3,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[4,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[5,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[6,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
 [,6] [,7] [,8] [,9] [,10] [,11]
[1,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[2,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[3,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[4,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[5,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[6,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
 [,12] [,13] [,14] [,15]
[1,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[2,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[3,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[4,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[5,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[6,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"

End(Not run)
```

---

c212.interim.1a.hier3 *A Three-Level Hierarchical Body-system based Model for interim analysis without Point-Mass.*

---

## Description

Implementation of a Three-Level Hierarchical Body-system based Model for interim analysis without Point-Mass.

## Usage

```
c212.interim.1a.hier3(trial.data, sim_type = "SLICE", burnin = 10000,
 iter = 40000, nchains = 3,
 global.sim.params = data.frame(type = c("MH", "SLICE"),
 param = c("sigma_MH", "w"), value = c(0.2,1), control = c(0,6),
 stringsAsFactors = FALSE),
 sim.params = NULL,
 monitor = data.frame(variable = c("theta", "gamma", "mu.gamma",
 "mu.theta", "sigma2.theta", "sigma2.gamma",
 "mu.theta.0", "mu.gamma.0", "tau2.theta.0", "tau2.gamma.0"),
 monitor = c(1, 1, 1, 1, 1, 1, 1, 1, 1, 1),
 stringsAsFactors = FALSE),
 initial_values = NULL,
 level = 1,
 hyper_params = list(mu.gamma.0.0 = 0, tau2.gamma.0.0 = 10,
 mu.theta.0.0 = 0, tau2.theta.0.0 = 10, alpha.gamma.0.0 = 3,
 beta.gamma.0.0 = 1, alpha.theta.0.0 = 3, beta.theta.0.0 = 1,
 alpha.gamma = 3, beta.gamma = 1,
 alpha.theta = 3, beta.theta = 1),
 memory_model = "HIGH")
```

## Arguments

|            |                                                                                                                                                                                                                                                                                                                            |
|------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data | A file or data frame containing the trial data. It must contain must contain the columns <i>I_index</i> (interval index), <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants in the trial arm). |
| sim_type   | The type of MCMC method to use for simulating from non-standard distributions. Allowed values are "MH" and "SLICE" for Metropolis_Hastings and Slice sampling respectively.                                                                                                                                                |
| burnin     | The burnin period for the monte-carlo simulation. These are discarded from the returned samples.                                                                                                                                                                                                                           |
| iter       | The total number of iterations for which the monte-carlo simulation is run. This includes the burnin period. The total number of samples returned is <i>iter - burnin</i>                                                                                                                                                  |
| nchains    | The number of independent chains to run.                                                                                                                                                                                                                                                                                   |

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>global.sim.params</code> | A data frame containing the parameters for the simulation type <i>sim_type</i> . For "MH" the parameter is the variance of the normal distribution used to simulate the next candidate value centred on the current value. For "SLICE" the parameters are the estimated width of the slice and a value limiting the search for the next sample.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <code>sim.params</code>        | A dataframe containing simulation parameters which override the global simulation parameters ( <i>global.sim.params</i> ) for particular model parameters. <i>sim.params</i> must contain the following columns: type: the simulation type ("MH" or "SLICE"); variable: the model parameter for which the simulation parameters are being overridden; B: the body-system (if applicable); AE: the adverse event (if applicable); param: the simulation parameter; value: the overridden value; control: the overridden control value.<br>The function <i>c212.sim.control.params</i> generates a template for <i>sim.params</i> which can be edited by the user.                                                                                                                                                                                                                                                 |
| <code>monitor</code>           | A dataframe indicating which sets of variables to monitor.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <code>initial_values</code>    | The initial values for starting the chains. If NULL (the default) is passed the function generates the initial values for the chains. <code>initial_values</code> is a list with the following format:<br><br><pre>list(gamma, theta, mu.gamma, mu.theta, sigma2.gamma,       sigma2.theta, mu.gamma.0, mu.theta.0, tau2.gamma.0,       tau2.theta.0)</pre> <p>where each element of the list is either a dataframe or array. The function <i>c212.gen.initial.values</i> can be used to generate a template for the list which can be updated by the user if required. The formats of the list elements are as follows:</p> <p><i>gamma, theta</i>: dataframe with columns <i>B, AE, chain, value</i><br/> <i>mu.gamma, mu.theta, sigma2.gamma, sigma2.theta</i>: dataframe with columns <i>B, chain, value</i><br/> <i>mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0</i>: array of size <i>chain</i>.</p> |
| <code>level</code>             | The level of longitudinal dependency between the intervals. 0 - independent intervals, 1 - common interval body-system means, 2 - weak dependency.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <code>hyper_params</code>      | The hyperparameters for the model. The default hyperparameters are those given in Berry and Berry 2004.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <code>memory_model</code>      | Allowed values are "HIGH" and "LOW". "HIGH" means use as much memory as possible. "LOW" means use the minimum amount of memory.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

## Details

The model is fitted by a Gibbs sampler. The posterior distributions for *gamma* and *theta* are sampled with either a Metropolis-Hastings step or a slice sampler.

## Value

The output from the simulation including all the sampled values is as follows:



```
list(id, sim_type, chains, nIntervals, Intervals, nBodySys, maxBs,
maxAEs, nAE, AE, B, burnin, iter, monitor,
mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0,
mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, gamma,
theta, gamma_acc, theta_acc)
```

where

*id* - a string identifying the version of the function

*sim\_type* - an string identifying the sampling method used for non-standard distributions, either "MH" or "SLICE"

*chains* - the number of chains for which the simulation was run.

*nIntervals* - the number of intervals in the simulation

*Intervals* - an array. The intervals.

*nBodySys* - the number of body-systems

*maxBs* - the maximum number of body-systems in an interval

*maxAEs* - the maximum number of AEs in a body-system

*nAE* - an array. The number of AEs in each body-system.

*AE* - an array of dimension *nBodySys*, *maxAEs*. The Adverse Events.

*B* - an array. The body-systems.

*burnin* - burnin used for the simulation.

*iter* - the total number of iterations in the simulation.

*monitor* - the variables being monitored. A dataframe.

*mu.gamma.0* - array of samples of dimension *chains*, *iter* - *burnin*

*mu.theta.0* - array of samples of dimension *chains*, *iter* - *burnin*

*tau2.gamma.0* - array of samples of dimension *chains*, *iter* - *burnin*

*tau2.theta.0* - array of samples of dimension *chains*, *iter* - *burnin*

*mu.gamma* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

*mu.theta* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

*sigma2.gamma* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

*sigma2.theta* - array of samples of dimension *chains*, *nBodySys* *iter* - *burnin*

*gamma* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*

*theta* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter* - *burnin*

*gamma\_acc* - the acceptance rate for the gamma samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

*theta\_acc* - the acceptance rate for the theta samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

## Note

The function performs the simulation and returns the raw output. No checks for convergence are performed.

**Author(s)**

R. Carragher

**Examples**

```

data(c212.trial.interval.data1)
raw = c212.interim.1a.hier3(c212.trial.interval.data1, level = 1, burnin = 100, iter = 200)
Not run:
data(c212.trial.interval.data1)
raw = c212.interim.1a.hier3(c212.trial.interval.data1, level = 1)

raw$B
 [,1] [,2] [,3] [,4] [,5]
[1,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[2,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[3,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[4,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[5,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[6,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
 [,6] [,7] [,8] [,9] [,10] [,11]
[1,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[2,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[3,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[4,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[5,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[6,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
 [,12] [,13] [,14] [,15]
[1,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[2,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[3,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[4,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[5,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[6,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"

End(Not run)

```

---

c212.interim.BB.hier2 *A Three-Level Hierarchical Body-system based Model for interim analysis with Point-Mass.*

---

**Description**

Implementation of a Three-Level Hierarchical Body-system based Model for interim analysis with Point-Mass.

**Usage**

```

c212.interim.BB.hier2(trial.data, sim_type = "SLICE", burnin = 20000,
 iter = 60000, nchains = 5, theta_algorithm = "MH",

```

```

global.sim.params = data.frame(type = c("MH", "MH", "MH", "MH",
"SLICE", "SLICE", "SLICE"),
param = c("sigma_MH_alpha", "sigma_MH_beta", "sigma_MH_gamma",
"sigma_MH_theta", "w_alpha", "w_beta", "w_gamma"),
value = c(3, 3, 0.2, 0.5, 1, 1, 1), control = c(0, 0, 0, 0, 6, 6, 6),
stringsAsFactors = FALSE),
sim.params = NULL,
monitor = data.frame(variable = c("theta", "gamma", "mu.gamma",
"mu.theta", "sigma2.theta", "sigma2.gamma", "pi"),
monitor = c(1, 1, 1, 1, 1, 1, 1), stringsAsFactors = FALSE),
initial_values = NULL, level = 1,
hyper_params = list(mu.gamma.0 = 0, tau2.gamma.0 = 10, mu.theta.0 = 0,
tau2.theta.0 = 10, alpha.gamma = 3, beta.gamma = 1, alpha.theta = 3,
beta.theta = 1, alpha.pi = 1.1, beta.pi = 1.1),
global.pm.weight = 0.5,
pm.weights = NULL,
adapt_phase=1, memory_model = "HIGH")

```

## Arguments

|                   |                                                                                                                                                                                                                                                                                                                                                 |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data        | A file or data frame containing the trial data. It must contain must contain the columns <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants).                                                                        |
| burnin            | The burnin period for the monte-carlo simulation. These are discarded from the returned samples.                                                                                                                                                                                                                                                |
| iter              | The total number of iterations for which the monte-carlo simulation is run. This includes the burnin period. The total number of samples returned is <i>iter - burnin</i>                                                                                                                                                                       |
| nchains           | The number of independent chains to run.                                                                                                                                                                                                                                                                                                        |
| theta_algorithm   | MCMC algorithm used to sample the theta variables. "MH" is the only currently supported stable algorithm.                                                                                                                                                                                                                                       |
| sim_type          | The type of MCMC method to use for simulating from non-standard distributions apart from theta. Allowed values are "MH" and "SLICE" for Metropolis_Hastings and Slice sampling respectively.                                                                                                                                                    |
| monitor           | A dataframe indicating which sets of variables to monitor.                                                                                                                                                                                                                                                                                      |
| global.sim.params | A data frame containing the parameters for the simulation type <i>sim_type</i> . For "MH" the parameter is the variance of the normal distribution used to simulate the next candidate value centred on the current value. For "SLICE" the parameters are the estimated width of the slice and a value limiting the search for the next sample. |
| sim.params        | A dataframe containing simulation parameters which override the global simulation parameters ( <i>global.sim.params</i> ) for particular model parameters. <i>sim.params</i> must contain the following columns: type: the simulation type ("MH" or "SLICE"); variable: the model parameter for which the simulation parameters are being       |

overridden; B: the body-system (if applicable); AE: the adverse event (if applicable); param: the simulation parameter; value: the overridden value; control: the overridden control value.

The function `c212.sim.control.params` generates a template for `sim.params` which can be edited by the user.

`initial_values` The initial values for starting the chains. If NULL (the default) is passed the function generates the initial values for the chains. `initial_values` is a list with the following format:

```
list(gamma, theta, mu.gamma, mu.theta, sigma2.gamma,
 sigma2.theta, pi, mu.gamma.0, mu.theta.0,
 tau2.gamma.0, tau2.theta.0, alpha.pi, beta.pi)
```

The function `c212.gen.initial.values` can be used to generate a template for the list which can be updated by the user if required. The formats of the list elements are as follows:

`gamma, theta`: dataframe with columns *B*, *AE*, *chain*, *value*

`mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, pi`: dataframe with columns *B*, *chain*, *value*

`level` Allowed values are 0, 1. Respectively these indicate independent intervals, common body-system means across the intervals.

`hyper_params` The hyperparameters for the model. The default hyperparameters are those given in Berry and Berry 2004.

`global.pm.weight` A global weighting for the proposal distribution used to sample theta.

`pm.weights` Override `global.pm.weight` for specific adverse events.

`adapt_phase` Unused parameter.

`memory_model` Allowed values are "HIGH" and "LOW". "HIGH" means use as much memory as possible. "LOW" means use the minimum amount of memory.

## Details

The model is fitted by a Gibbs sampler. The details of the complete conditional densities are given in Berry and Berry (2004).

## Value

The output from the simulation including all the sampled values is as follows:

```
list(id, theta_alg, sim_type, chains, nIntervals, Intervals, nBodySys,
 maxBs, maxAEs, nAE, AE, B, burnin,
 iter, monitor,
 mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, pi,
 gamma, theta, gamma_acc, theta_acc)
```

where

*id* - a string identifying the version of the function

*theta\_alg* - an string identifying the algorithm used to sample theta

*sim\_type* - an string identifying the sampling method used for non-standard distributions, either "MH" or "SLICE"

*chains* - the number of chains for which the simulation was run

*nIntervals* - the number of intervals in the simulation

*Intervals* - an array. The intervals.

*nBodySys* - the number of body-systems

*maxBs* - the maximum number of body-systems in an interval

*maxAEs* - the maximum number of AEs in a body-system

*nAE* - an array. The number of AEs in each body-system.

*AE* - an array of dimension *nBodySys*, *maxAEs*. The Adverse Events.

*B* - an array. The body-systems.

*burnin* - burnin used for the simulation.

*iter* - the total number of iterations in the simulation.

*monitor* - the variables being monitored. A dataframe.

*mu.gamma* - array of samples of dimension *chains*, *nBodySys iter - burnin*

*mu.theta* - array of samples of dimension *chains*, *nBodySys iter - burnin*

*sigma2.gamma* - array of samples of dimension *chains*, *nBodySys iter - burnin*

*sigma2.theta* - array of samples of dimension *chains*, *nBodySys iter - burnin*

*pi* - array of samples of dimension *chains*, *nBodySys iter - burnin*

*gamma* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter - burnin*

*theta* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter - burnin*

*gamma\_acc* - the acceptance rate for the gamma samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

*theta\_acc* - the acceptance rate for the theta samples. An array of dimension *chains*, *nBodySys*, *maxAEs*

**Note**

The function performs the simulation and returns the raw output. No checks for convergence are performed.

**Author(s)**

R. Carragher

**Examples**

```

data(c212.trial.interval.data1)
raw = c212.interim.1a.hier2(c212.trial.interval.data1, level = 1, burnin = 100, iter = 200)

Not run:
data(c212.trial.interval.data1)
raw = c212.interim.1a.hier2(c212.trial.interval.data1, level = 1)

raw$B
 [,1] [,2] [,3] [,4] [,5]
[1,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[2,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[3,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[4,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[5,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[6,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
 [,6] [,7] [,8] [,9] [,10] [,11]
[1,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[2,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[3,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[4,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[5,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[6,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
 [,12] [,13] [,14] [,15]
[1,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[2,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[3,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[4,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[5,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[6,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"

End(Not run)

```

---

c212.interim.BB.hier3 *A Three-Level Hierarchical Body-system based Model for interim analysis with Point-Mass.*

---

**Description**

Implementation of a Three-Level Hierarchical Body-system based Model for interim analysis with Point-Mass.

**Usage**

```

c212.interim.BB.hier3(trial.data, sim_type = "SLICE", burnin = 20000,
 iter = 60000, nchains = 5, theta_algorithm = "MH",
 global.sim.params = data.frame(type = c("MH", "MH", "MH", "MH",
 "SLICE", "SLICE", "SLICE"),

```

```

param = c("sigma_MH_alpha", "sigma_MH_beta", "sigma_MH_gamma",
"sigma_MH_theta", "w_alpha", "w_beta", "w_gamma"),
value = c(3, 3, 0.2, 0.25, 1, 1, 1), control = c(0, 0, 0, 0, 6, 6, 6),
stringsAsFactors = FALSE),
sim.params = NULL,
monitor = data.frame(variable = c("theta", "gamma", "mu.gamma", "mu.theta",
"sigma2.theta", "sigma2.gamma",
"mu.theta.0", "mu.gamma.0", "tau2.theta.0", "tau2.gamma.0",
"pi", "alpha.pi", "beta.pi"),
monitor = c(1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1),
stringsAsFactors = FALSE),
initial_values = NULL, level = 1, hyper_params = list(mu.gamma.0.0 = 0,
tau2.gamma.0.0 = 10, mu.theta.0.0 = 0, tau2.theta.0.0 = 10,
alpha.gamma.0.0 = 3, beta.gamma.0.0 = 1, alpha.theta.0.0 = 3,
beta.theta.0.0 = 1, alpha.gamma = 3,
beta.gamma = 1, alpha.theta = 3, beta.theta = 1,
lambda.alpha = 1.0, lambda.beta = 1.0),
global.pm.weight = 0.5,
pm.weights = NULL,
adapt_phase=1, memory_model = "HIGH")

```

## Arguments

|                   |                                                                                                                                                                                                                                                                                                                                                 |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data        | A file or data frame containing the trial data. It must contain must contain the columns <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants).                                                                        |
| burnin            | The burnin period for the monte-carlo simulation. These are discarded from the returned samples.                                                                                                                                                                                                                                                |
| iter              | The total number of iterations for which the monte-carlo simulation is run. This includes the burnin period. The total number of samples returned is <i>iter - burnin</i>                                                                                                                                                                       |
| nchains           | The number of independent chains to run.                                                                                                                                                                                                                                                                                                        |
| theta_algorithm   | MCMC algorithm used to sample the theta variables. "MH" is the only currently supported stable algorithm.                                                                                                                                                                                                                                       |
| sim_type          | The type of MCMC method to use for simulating from non-standard distributions apart from theta. Allowed values are "MH" and "SLICE" for Metropolis_Hastings and Slice sampling respectively.                                                                                                                                                    |
| monitor           | A dataframe indicating which sets of variables to monitor.                                                                                                                                                                                                                                                                                      |
| global.sim.params | A data frame containing the parameters for the simulation type <i>sim_type</i> . For "MH" the parameter is the variance of the normal distribution used to simulate the next candidate value centred on the current value. For "SLICE" the parameters are the estimated width of the slice and a value limiting the search for the next sample. |
| sim.params        | A dataframe containing simulation parameters which override the global simulation parameters ( <i>global.sim.params</i> ) for particular model parameters. <i>sim.params</i> must contain the following columns: type: the simulation type ("MH" or "SLICE");                                                                                   |

variable: the model parameter for which the simulation parameters are being overridden; B: the body-system (if applicable); AE: the adverse event (if applicable); param: the simulation parameter; value: the overridden value; control: the overridden control value.

The function `c212.sim.control.params` generates a template for `sim.params` which can be edited by the user.

`initial_values` The initial values for starting the chains. If NULL (the default) is passed the function generates the initial values for the chains. `initial_values` is a list with the following format:

```
list(gamma, theta, mu.gamma, mu.theta, sigma2.gamma,
 sigma2.theta, pi, mu.gamma.0, mu.theta.0,
 tau2.gamma.0, tau2.theta.0, alpha.pi, beta.pi)
```

The function `c212.gen.initial.values` can be used to generate a template for the list which can be updated by the user if required. The formats of the list elements are as follows:

`gamma, theta`: dataframe with columns `B`, `AE`, `chain`, `value`

`mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, pi`: dataframe with columns `B`, `chain`, `value`

`mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0, alpha.pi, beta.pi`: array of size `chain`.

`level` Allowed values are 0, 1, 2. Respectively these indicate independent intervals, common body-system means across the intervals and weak relationships between the intervals.

`hyper_params` The hyperparameters for the model. The default hyperparameters are those given in Berry and Berry 2004.

`global.pm.weight`

A global weighting for the proposal distribution used to sample theta.

`pm.weights`

Override `global.pm.weight` for specific adverse events.

`adapt_phase`

Unused parameter.

`memory_model`

Allowed values are "HIGH" and "LOW". "HIGH" means use as much memory as possible. "LOW" means use the minimum amount of memory.

## Details

The model is fitted by a Gibbs sampler. The details of the complete conditional densities are given in Berry and Berry (2004).

## Value

The output from the simulation including all the sampled values is as follows:

```
list(id, theta_alg, sim_type, chains, nIntervals, Intervals, nBodySys,
 maxBs, maxAEs, nAE, AE, B, burnin,
 iter, monitor, mu.gamma.0, mu.theta.0, tau2.gamma.0, tau2.theta.0,
 mu.gamma, mu.theta, sigma2.gamma, sigma2.theta, pi, alpha.pi, beta.pi,
 alpha.pi_acc, beta.pi_acc, gamma, theta, gamma_acc, theta_acc)
```



where

*id* - a string identifying the version of the function

*theta\_alg* - an string identifying the algorithm used to sample theta

*sim\_type* - an string identifying the sampling method used for non-standard distributions, either "MH" or "SLICE"

*chains* - the number of chains for which the simulation was run

*nIntervals* - the number of intervals in the simulation

*Intervals* - an array. The intervals.

*nBodySys* - the number of body-systems

*maxBs* - the maximum number of body-systems in an interval

*maxAEs* - the maximum number of AEs in a body-system

*nAE* - an array. The number of AEs in each body-system.

*AE* - an array of dimension *nBodySys*, *maxAEs*. The Adverse Events.

*B* - an array. The body-systems.

*burnin* - burnin used for the simulation.

*iter* - the total number of iterations in the simulation.

*monitor* - the variables being monitored. A dataframe.

*mu.gamma.0* - array of samples of dimension *chains*, *iter - burnin*

*mu.theta.0* - array of samples of dimension *chains*, *iter - burnin*

*tau2.gamma.0* - array of samples of dimension *chains*, *iter - burnin*

*tau2.theta.0* - array of samples of dimension *chains*, *iter - burnin*

*mu.gamma* - array of samples of dimension *chains*, *nBodySys iter - burnin*

*mu.theta* - array of samples of dimension *chains*, *nBodySys iter - burnin*

*sigma2.gamma* - array of samples of dimension *chains*, *nBodySys iter - burnin*

*sigma2.theta* - array of samples of dimension *chains*, *nBodySys iter - burnin*

*pi* - array of samples of dimension *chains*, *nBodySys iter - burnin* *alpha.pi* - array of samples of dimension *chains*, *iter - burnin* *beta.pi* - array of samples of dimension *chains*, *iter - burnin*

*alpha.pi\_acc* - the acceptance rate for the alpha.pi samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *maxAEs*

*beta.pi\_acc* - the acceptance rate for the beta.pi samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *maxAEs*

*gamma* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter - burnin*

*theta* - array of samples of dimension *chains*, *nBodySys*, *maxAEs*, *iter - burnin*

*gamma\_acc* - the acceptance rate for the gamma samples if a Metropolis-Hastings method is used. An array of dimension *chains*, *nBodySys*, *maxAEs*

*theta\_acc* - the acceptance rate for the theta samples. An array of dimension *chains*, *nBodySys*, *maxAEs*

**Note**

The function performs the simulation and returns the raw output. No checks for convergence are performed.

**Author(s)**

R. Carragher

**Examples**

```
data(c212.trial.interval.data1)
raw = c212.interim.BB.hier3(c212.trial.interval.data1, level = 1, burnin = 100, iter = 200)

Not run:
data(c212.trial.interval.data1)
raw = c212.interim.BB.hier3(c212.trial.interval.data1, level = 1)

raw$B
 [,1] [,2] [,3] [,4] [,5]
[1,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[2,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[3,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[4,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[5,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
[6,] "Bdy-sys_1" "Bdy-sys_10" "Bdy-sys_11" "Bdy-sys_12" "Bdy-sys_13"
 [,6] [,7] [,8] [,9] [,10] [,11]
[1,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[2,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[3,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[4,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[5,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
[6,] "Bdy-sys_14" "Bdy-sys_15" "Bdy-sys_2" "Bdy-sys_3" "Bdy-sys_4" "Bdy-sys_5"
 [,12] [,13] [,14] [,15]
[1,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[2,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[3,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[4,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[5,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"
[6,] "Bdy-sys_6" "Bdy-sys_7" "Bdy-sys_8" "Bdy-sys_9"

End(Not run)
```

---

c212.interim.MLE

*Poisson Maximum Likelihood Estimator*

---

**Description**

Calculate the Poisson Maximum Likelihood Estimator for interim analysis data.

**Usage**

```
c212.interim.MLE(trial.data)
```

**Arguments**

`trial.data` A file or data frame containing the trial data. It must contain must contain the columns *I\_index* (interval index), *B* (body-system), *AE* (adverse event), *Group* (1 - control, 2 treatment), *Count* (total number of events), *Total* (total number of participants in the trial arm).

**Value**

The maximum likelihood estimators and summary statistics.

**Author(s)**

R. Carragher

**Examples**

```
data(c212.trial.interval.data1)
data <- c212.trial.interval.data1[c212.trial.interval.data1$Interval == "0.0-180.0",]
raw = c212.interim.MLE(data)
Not run:
data(c212.trial.interval.data1)
raw = c212.interim.MLE(c212.trial.interval.data1)

End(Not run)
```

---

c212.LSL *Implementaion of the least-slope estimator estimator (LSL) for the proportion of true null hypotheses.*

---

**Description**

The least-slope estimator estimator (LSL) is one of a number of estimators of the proportion of true null hypotheses. This implementation assumes a grouped structure for the data.

**Usage**

```
c212.LSL(trial.data)
```

**Arguments**

`trial.data` Data frame containing the p-values for the hypotheses being tested. The data must contain the following columns: *B*: the index or name of the groupings; *p*: the p-values of the hypotheses.

**Value**

An estimate of the proportion of true null hypotheses.

**Note**

The implementation is that described in Hu, J. X. and Zhao, H. and Zhou, H. H. (2010).

**Author(s)**

R. Carragher<raymond.carragher@strath.ac.uk>

**References**

Hu, J. X. and Zhao, H. and Zhou, H. H. (2010). False Discovery Rate Control With Groups. J Am Stat Assoc, 105(491):1215-1227.

Benjamini Y, Hochberg Y. (2000). On the Adaptive Control of the False Discovery Rate in Multiple Testing With Independent Statistics. Journal of Educational and Behavioral Statistics, 25(1):60–83.

**Examples**

```
data(c212.FDR.data)
lsl <- c212.LSL(c212.FDR.data)
print(lsl)
Not run:
 B pi0
1 Bdy-sys_5 1.0000000
2 Bdy-sys_6 1.0000000
3 Bdy-sys_7 1.0000000
4 Bdy-sys_8 1.0000000
5 Bdy-sys_2 1.0000000
6 Bdy-sys_3 0.2857143
7 Bdy-sys_4 1.0000000
8 Bdy-sys_1 1.0000000

End(Not run)
```

---

c212.monitor.samples *Generate a template for choosing which samples to monitor.*

---

**Description**

This function generate a template for choosing which samples to monitor based on the model and hierarchy. As some of the MCMC model simulations require large amounts of memory choosing not to monitor samples reduced the overall memory footprint.

**Usage**

```
c212.monitor.samples(model = "1a", hier = 3)
```

**Arguments**

model Allowed values are "1a" and "BB". "BB" models include a point-mass.  
 hier Allowed values are 2 and 3. Generate a template for a 2 or 3 level hierarchy.

**Value**

A dataframe containing two columns:

*variable*: the name of a class of variables e.g. "theta" *monitor*: 0 - don't monitor, 1 - monitor.

**Author(s)**

R. Carragher

**Examples**

```
c212.monitor.samples("1a", hier = 3)
Not run:
c212.monitor.samples("1a", hier = 3)
 variable monitor
1 theta 1
2 gamma 0
3 mu.gamma 0
4 mu.theta 0
5 sigma2.theta 0
6 sigma2.gamma 0
7 mu.theta.0 0
8 mu.gamma.0 0
9 tau2.theta.0 0
10 tau2.gamma.0 0

End(Not run)
```

---

c212.NOADJ

*Unadjusted test of multiple hypotheses.*

---

**Description**

Unadjusted test of multiple hypotheses.

**Usage**

```
c212.NOADJ(trial.data, alpha = 0.05)
```

**Arguments**

trial.data File or data frame containing the p-values for the hypotheses being tested. The data must include a column called *p* which contains the p-values of the hypotheses.  
 alpha The level for FDR control. E.g. 0.05.

**Value**

The subset of hypotheses in *file* or *trial.data* deemed significant at level *alpha*.

**Note**

No check is made for duplicate rows in the input file or data frame.

**Author(s)**

R. Carragher

**Examples**

```
trial.data <- data.frame(B = c(1, 2, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 4, 4),
 j = c(1, 1, 2, 3, 4, 1, 2, 3, 4, 5, 6, 7, 1, 2, 3, 4, 5),
 AE = c("AE1", "AE2", "AE3", "AE4", "AE5", "AE6", "AE7", "AE8", "AE9", "AE10", "AE11",
 "AE12", "AE13", "AE14", "AE15", "AE16", "AE17"),
 p = c(0.135005, 0.010000, 0.001000, 0.005000, 0.153501, 0.020000, 0.0013, 0.0023,
 0.011, 0.023000, 0.016, 0.0109, 0.559111, 0.751986, 0.308339, 0.837154, 0.325882))
```

```
c212.NOADJ(trial.data, alpha=0.05)
```

```
Not run:
```

```
 B j AE p
1 2 2 AE3 0.0010
2 3 2 AE7 0.0013
3 3 3 AE8 0.0023
4 2 3 AE4 0.0050
5 2 1 AE2 0.0100
6 3 7 AE12 0.0109
7 3 4 AE9 0.0110
8 3 6 AE11 0.0160
9 3 1 AE6 0.0200
10 3 5 AE10 0.0230
```

```
End(Not run)
```

---

c212.plot.eot.data      *Plot Adverse Event Incidence Data*

---

**Description**

This function plots a graph of the total adverse event incidence counts by body-system and by individual adverse event for end of trial data.

**Usage**

```
c212.plot.eot.data(trial.data, legend = TRUE, interactive = FALSE,
 cex = 0.5)
```

**Arguments**

|             |                                                                                                                                                                                                                                                                         |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data  | A file or data frame containing the trial data. The data frame must contain the columns <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Total</i> (total number of participants). |
| legend      | Boolean. If TRUE print a legend.                                                                                                                                                                                                                                        |
| interactive | Boolean. If TRUE allow the user to identify individual adverse events on the individual adverse events graph.                                                                                                                                                           |
| cex         | Font size of the labels on the Adverse Event counts graph.                                                                                                                                                                                                              |

**Details**

Two graphs are displayed on the same panel. The top graph is of AE Incidence Counts by Body-System. The lower graphs is of the Individual AE Incidence Counts.

**Value**

Nothing is returned.

**Note**

The legend may obscure a portion of the graph. In this case the legend may be suppressed by choosing *legend = FALSE* when calling the function.

**Author(s)**

R. Carragher

**Examples**

```
Not run:
data(c212.trial.data)
c212.plot.eot.data(c212.trial.data)

End(Not run)
```

---

c212.plot.interim.data.rd

*Plot Adverse Event Count Data for a Body-system by Interval*

---

**Description**

Plot adverse event interval data for a body-system.

**Usage**

```
c212.plot.interim.data(trial.data, body_sys, cex = 0.8, title = NULL)
```

**Arguments**

|                         |                                                                                                                                                                                                                                                                                                                           |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>trial.data</code> | A file or data frame containing the trial data. The data frame must contain the columns <i>I_index</i> (interval), <i>B</i> (body-system), <i>AE</i> (adverse event), <i>Group</i> (1 - control, 2 treatment), <i>Count</i> (total number of events), <i>Exposure</i> (total time of participants spent in the interval). |
| <code>body_sys</code>   | The body-system for which to plot the events.                                                                                                                                                                                                                                                                             |
| <code>cex</code>        | Font size of the labels on the Adverse Event counts graph.                                                                                                                                                                                                                                                                |
| <code>title</code>      | Main title of the graph.                                                                                                                                                                                                                                                                                                  |

**Details**

This function plots a graph of the count of adverse events which have occurred in an interval for a particular body-system by interval.

**Value**

Nothing is returned.

**Author(s)**

R. Carragher

**Examples**

```
Not run:
data(c212.trial.interval.data1)
c212.plot.interim.data(c212.trial.interval.data1, "Bdy-sys_3")

End(Not run)
```

---

c212.plot.samples      *Plot Posterior Distribution*

---

**Description**

This function plots a graph of the sampled posterior distribution.

**Usage**

```
c212.plot.samples(samples, title)
```

**Arguments**

|                      |                                               |
|----------------------|-----------------------------------------------|
| <code>samples</code> | An array of samples indexed by <i>chain</i> . |
| <code>title</code>   | The graph title.                              |



**Details**

Two graphs are displayed on the same panel. The left graph is the traceplot of the chains. The right graph is a plot of the distribution.

**Value**

Nothing is returned.

**Author(s)**

R. Carragher

**Examples**

```
Not run:
data(c212.trial.data)
raw = c212.1a(c212.trial.data)
sample = raw$theta[,2,2,]
c212.plot.samples(sample, sprintf("%s: %s %s", "theta", raw$B[2], raw$AE[2]))

End(Not run)
```

---

c212.pointmass.weights

*Generate a template for the point-mass weightings.*

---

**Description**

This function generate a template for weights for the proposal distribution used to sample *theta* variables in models which use a point-mass.

**Usage**

```
c212.pointmass.weights(trial.data)
```

**Arguments**

`trial.data` A file or data frame containing the trial data, either for end of trial or interim analysis.

**Value**

A dataframe containing the weightings template for each Body-system, adverse event and, if required, interval.

**Author(s)**

R. Carragher

## Examples

```
data(c212.trial.data)
pmw <- c212.pointmass.weights(c212.trial.data)
head(pmw)
Not run:
data(c212.trial.data)
pmw <- c212.pointmass.weights(c212.trial.data)
head(pmw)
 B AE weight_pm
1 Bdy-sys_2 Adv-Ev_5 0.5
2 Bdy-sys_5 Adv-Ev_24 0.5
3 Bdy-sys_6 Adv-Ev_31 0.5
4 Bdy-sys_8 Adv-Ev_42 0.5
5 Bdy-sys_7 Adv-Ev_39 0.5
6 Bdy-sys_6 Adv-Ev_34 0.5

End(Not run)
```

---

```
c212.print.convergence.summary
```

*Print a Summary of the Convergence Diagnostics of the Simulation*

---

## Description

The function prints the maximum and minimum values of either Gelman-Rubin diagnostic or the Geweke diagnostic for each group of samples, e.g. theta, gamma, mu.gamma etc.

## Usage

```
c212.print.convergence.summary(conv)
```

## Arguments

conv            The output from a call to *c212.convergence.diag*.

## Value

Nothing

## Note

The Geweke statistic is a Z-score calculated from a single chain. Due to the large number of variables sampled it is possible that a certain number will be deemed significant (at the 5% level) even though the simulation may have converged.

## Author(s)

R. Carragher

**Examples**

```
data(c212.trial.data)
raw = c212.BB(c212.trial.data, burnin = 100, iter = 200)
conv = c212.convergence.diag(raw)
c212.print.convergence.summary(conv)
Not run:
data(c212.trial.data)
raw = c212.BB(c212.trial.data)
conv = c212.convergence.diag(raw)
c212.print.convergence.summary(conv)

End(Not run)
```

---

c212.print.summary.stats

*Print the Summary Statistics of Posterior Distributions*

---

**Description**

The function prints the variable names, the mean, the 95 MCMC standard error for the simulated sample.

**Usage**

```
c212.print.summary.stats(summ)
```

**Arguments**

summ                    The output from a call to *c212.summary.stats*.

**Value**

Nothing

**Author(s)**

R. Carragher

**Examples**

```
data(c212.trial.data)
raw = c212.BB(c212.trial.data, burnin = 100, iter = 200)
summ = c212.summary.stats(raw)
c212.print.summary.stats(summ)
Not run:
data(c212.trial.data)
raw = c212.BB(c212.trial.data, burnin = 100, iter = 200)
summ = c212.summary.stats(raw)
c212.print.summary.stats(summ)
```

```
End(Not run)
```

---

|             |                                                                                                                                |
|-------------|--------------------------------------------------------------------------------------------------------------------------------|
| c212.ptheta | <i>Reports the posterior probability that theta (the increase in the log-odds) is greater than zero for each Adverse Event</i> |
|-------------|--------------------------------------------------------------------------------------------------------------------------------|

---

### Description

This function reports the posterior probability that theta is positive, i.e. that there is an increase in log odds of an adverse event being associated with treatment.

### Usage

```
c212.ptheta(raw)
```

### Arguments

|     |                                    |
|-----|------------------------------------|
| raw | The output from a call to c212.BB. |
|-----|------------------------------------|

### Value

A data frame containing the columns: *interval* if analysing interim data, *B*: body system, *AE*: adverse event and *ptheta*, the posterior probability that theta is positive.

### Author(s)

R. Carragher

### Examples

```
data(c212.trial.data)
raw = c212.BB(c212.trial.data, burnin = 100, iter = 200)
p = c212.ptheta(raw)
head(p)

Not run:
data(c212.trial.data)
raw = c212.BB(c212.trial.data)

End(Not run)

Not run:
p = c212.ptheta(raw)

head(p)
 B AE ptheta
1 Bdy-sys_1 Adv-Ev_1 0.2560500
2 Bdy-sys_2 Adv-Ev_2 0.9426417
```

```

3 Bdy-sys_2 Adv-Ev_3 0.8751500
4 Bdy-sys_2 Adv-Ev_4 0.1154917
5 Bdy-sys_2 Adv-Ev_5 0.2317417
6 Bdy-sys_3 Adv-Ev_6 1.0000000

```

```
End(Not run)
```

---

```
c212.sim.control.params
```

*Generate a template for the individual model parameter simulation control parameters.*

---

## Description

This function generates a template for overriding the global simulation parameters used by the model simulation functions (e.g. c212.BB).

## Usage

```
c212.sim.control.params(trial.data, model = "1a")
```

## Arguments

|            |                                                                                              |
|------------|----------------------------------------------------------------------------------------------|
| trial.data | A file or data frame containing the trial data, either for end of trial or interim analysis. |
| model      | Allowed values are "BB" and "1a" for point-mass and non-point-mass models respectively.      |

## Value

A dataframe containing the simulation parameters template.

## Author(s)

R. Carragher

## Examples

```

data(c212.trial.data)
s.p <- c212.sim.control.params(c212.trial.data)
head(s.p)
Not run:
data(c212.trial.data)
s.p <- c212.sim.control.params(c212.trial.data)
head(s.p)

```

|   | type  | variable | B         | AE param  | value | control |
|---|-------|----------|-----------|-----------|-------|---------|
| 1 | SLICE | gamma    | Bdy-sys_2 | Adv-Ev_5  | w     | 1 6     |
| 2 | SLICE | gamma    | Bdy-sys_5 | Adv-Ev_24 | w     | 1 6     |

```

3 SLICE gamma Bdy-sys_6 Adv-Ev_31 w 1 6
4 SLICE gamma Bdy-sys_8 Adv-Ev_42 w 1 6
5 SLICE gamma Bdy-sys_7 Adv-Ev_39 w 1 6
6 SLICE gamma Bdy-sys_6 Adv-Ev_34 w 1 6

```

```
End(Not run)
```

---

```

c212.ssBH Implementation of Subset Benjamini-Hochberg for False Discover
Rate control

```

---

## Description

The Subset Benjamini-Hochberg allows for the use of subsets to allow the extension of the Benjamini-Hochberg procedure to types of non-positively dependent regression statistics.

## Usage

```
c212.ssBH(trial.data, alpha = 0.05)
```

## Arguments

|                         |                                                                                                                                                                                                            |
|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>trial.data</code> | File or data frame containing the p-values for the hypotheses being tested. The data must contain the following columns: <i>B</i> : the index of the groupings; <i>p</i> : the p-values of the hypotheses. |
| <code>alpha</code>      | The level for FDR control. E.g. 0.05.                                                                                                                                                                      |

## Value

The subset of hypotheses in *file* or *trial.data* deemed significant by the Subset Benjamini-Hochberg process.

## Note

This process is at most as powerful as the Benjamini-Hochberg procedure. The subsets do not have to be disjoint.

## Author(s)

R. Carragher

## References

Yekutieli, Daniel (2008). False discovery rate control for non-positively regression dependent test statistics. *Journal of Statistical Planning and Inference*, 138(2):405-415.

**Examples**

```

trial.data <- data.frame(B = c(1, 2, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 4, 4, 4, 4, 4),
 j = c(1, 1, 2, 3, 4, 1, 2, 3, 4, 5, 6, 7, 1, 2, 3, 4, 5),
 AE = c("AE1", "AE2", "AE3", "AE4", "AE5", "AE6", "AE7", "AE8", "AE9", "AE10", "AE11",
 "AE12", "AE13", "AE14", "AE15", "AE16", "AE17"),
 p = c(0.135005, 0.010000, 0.001000, 0.005000, 0.153501, 0.020000, 0.0013, 0.0023,
 0.011, 0.023000, 0.016, 0.0109, 0.559111, 0.751986, 0.308339, 0.837154, 0.325882))

c212.ssBH(trial.data, alpha=0.05)

Not run:
 B j AE p
1 2 2 AE3 0.0010
2 2 3 AE4 0.0050
3 3 2 AE7 0.0013
4 3 3 AE8 0.0023
5 3 7 AE12 0.0109
6 3 4 AE9 0.0110

End(Not run)

```

---

c212.summary.stats      *Summary Statistics for the Posterior Distributions in the model.*

---

**Description**

Returns the Summary Statistics for the Posterior Distributions in the model.

**Usage**

```
c212.summary.stats(raw)
```

**Arguments**

`raw`                      The output from a model simulation (e.g. c212.BB).

**Details**

The function reports the mean, upper and lower bounds of the 95 standard deviation and MCMC standard error.

**Value**

Returns a list of the summary statistics for each sampled variable. Each element of the list is a data.frame containing at least the columns *mean*, *hpi\_lower*, *hpi\_upper*, *SD* and *SE*. For the simulation return by *c212.Ia* the output is as follows:

```
list(theta.summary, gamma.summary, mu.gamma.summary,
 mu.theta.summary = mu.theta_summ,
 sigma2.gamma.summary, sigma2.theta.summary,
 mu.gamma.0.summary, mu.theta.0.summary,
 tau2.gamma.0.summary, tau2.theta.0.summary)
```

Additional columns which may be used to identify the individual variables are *B*, the body-system, and *AE*, the Adverse Event and *interval*.

### Note

The MCMC error is found using the 'coda' summary function.

### Author(s)

R. Carragher

### Examples

```
data(c212.trial.data)
raw = c212.BB(c212.trial.data, burnin = 100, iter = 200)
summ = c212.summary.stats(raw)
Not run:
data(c212.trial.data)
raw = c212.BB(c212.trial.data)
summ = c212.summary.stats(raw)

End(Not run)
```

---

c212.trial.data

*End of Trial Data Clinical Data for Adverse Event Incidence*

---

### Description

This data set contains the counts of adverse event incidence for the trial.

### Usage

```
data(c212.trial.data)
```

### Format

A dataframe with columns *B* - body-system, *AE* - adverse event, *Group* - 1 for control, 2 for treatment, *Count* - total adverse event incidence, *Total* - total patients on the trial arm. The dataframe contains 90 observations.



---

`c212.trial.interval.data1`*Interim analysis trial data.*

---

**Description**

This data set contains count of the adverse events over the first two intervals of a clinical trial.

**Usage**

```
data(c212.trial.interval.data1)
```

**Format**

A dataframe with columns *interval*, *I\_index* - the interval order, *B* - body-system, *AE* - adverse event, *Group* - 1 for control, 2 for treatment, *Count* - total adverse events that occurred in the interval, *Exposure* - the total time all at risk subjects spent in the interval. The dataframe contains 1860 observations.

---

`c212.trial.interval.data2`*Interim analysis trial data.*

---

**Description**

This data set contains count of the adverse events over all intervals of a clinical trial.

**Usage**

```
data(c212.trial.interval.data2)
```

**Format**

A dataframe with columns *interval*, *I\_index* - the interval order, *B* - body-system, *AE* - adverse event, *Group* - 1 for control, 2 for treatment, *Count* - total adverse events that occurred in the interval, *Exposure* - the total time all at risk subjects spent in the interval. The dataframe contains 3100 observations.

---

|          |                                                                                                   |
|----------|---------------------------------------------------------------------------------------------------|
| c212.TST | <i>Implementaion of the two-stage estimator (TST) for the proportion of true null hypotheses.</i> |
|----------|---------------------------------------------------------------------------------------------------|

---

### Description

The two-stage estimator (TST) is one of a number of estimators of the proportion of true null hypotheses. It uses the Benjamini-Hochberg procedure at a reduced level to make the estimate. This implementation assumes a grouped structure for the data.

### Usage

```
c212.TST(trial.data, alpha)
```

### Arguments

|            |                                                                                                                                                                                                            |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| trial.data | Data frame containing the p-values for the hypotheses being tested. The data must contain the following columns: <i>B</i> : the index or name of the groupings; <i>p</i> : the p-values of the hypotheses. |
| alpha      | The level for FDR control. E.g. 0.05.                                                                                                                                                                      |

### Value

An estimate of the proportion of true null hypotheses.

### Note

The implementation is that described in Hu, J. X. and Zhao, H. and Zhou, H. H. (2010).

### Author(s)

R. Carragher<raymond.carragher@strath.ac.uk>

### References

Hu, J. X. and Zhao, H. and Zhou, H. H. (2010). False Discovery Rate Control With Groups. *J Am Stat Assoc*, 105(491):1215-1227.

Y. Benjamini, A. M. Krieger, and D. Yekutieli (2006). Adaptive linear step-up procedures that control the false discovery rate. *Biometrika*, 93(3):491–507.

### Examples

```
data(c212.FDR.data)
c212.TST(c212.FDR.data)
Not run:
 B pi0
1 Bdy-sys_5 1.0
2 Bdy-sys_6 1.0
```

```
3 Bdy-sys_7 1.0
4 Bdy-sys_8 1.0
5 Bdy-sys_2 0.5
6 Bdy-sys_3 0.0
7 Bdy-sys_4 1.0
8 Bdy-sys_1 1.0

End(Not run)
```

# Index

- \* **Adverse Event**
  - c212-package, 3
- \* **BH adjusted p-values**
  - c212.BH.adjust.pvals, 21
- \* **BH**
  - c212.BH, 19
  - c212.err.cntrl, 28
- \* **BONF**
  - c212.err.cntrl, 28
- \* **Bayesian Hierarchy**
  - c212-package, 3
- \* **Bayesian**
  - c212.1a, 4
  - c212.1a.interim, 7
  - c212.BB, 11
  - c212.BB.interim, 15
  - c212.convergence.diag, 25
  - c212.gen.initial.values, 32
  - c212.global.sim.params, 33
  - c212.hyper.params, 34
  - c212.interim.1a.hier2, 35
  - c212.interim.1a.hier3, 39
  - c212.interim.BB.hier2, 42
  - c212.interim.BB.hier3, 46
  - c212.monitor.samples, 52
  - c212.plot.eot.data, 54
  - c212.plot.interim.data.rd, 55
  - c212.plot.samples, 56
  - c212.pointmass.weights, 57
  - c212.print.convergence.summary, 58
  - c212.print.summary.stats, 59
  - c212.ptheta, 60
  - c212.sim.control.params, 61
  - c212.summary.stats, 63
- \* **Benjamini-Hochberg adjusted p-values**
  - c212.BH.adjust.pvals, 21
- \* **Benjamini-Hochberg**
  - c212.BH, 19
- \* **Berry and Berry**
  - c212.1a, 4
  - c212.1a.interim, 7
  - c212.BB, 11
  - c212.BB.interim, 15
  - c212.convergence.diag, 25
  - c212.gen.initial.values, 32
  - c212.global.sim.params, 33
  - c212.hyper.params, 34
  - c212.interim.1a.hier2, 35
  - c212.interim.1a.hier3, 39
  - c212.interim.BB.hier2, 42
  - c212.interim.BB.hier3, 46
  - c212.monitor.samples, 52
  - c212.plot.eot.data, 54
  - c212.plot.interim.data.rd, 55
  - c212.pointmass.weights, 57
  - c212.print.convergence.summary, 58
  - c212.print.summary.stats, 59
  - c212.ptheta, 60
  - c212.sim.control.params, 61
  - c212.summary.stats, 63
- \* **Berry**
  - c212-package, 3
- \* **Body-system**
  - c212-package, 3
- \* **Bonferroni**
  - c212.BONF, 24
- \* **DFDR**
  - c212-package, 3
  - c212.DFDR, 27
  - c212.err.cntrl, 28
- \* **Double False Discovery Rate**
  - c212-package, 3
  - c212.DFDR, 27
- \* **Exact**
  - c212.fisher.test, 30
- \* **FDR**
  - c212-package, 3
- \* **FWER**

- c212.BONF, [24](#)
- \* **False Discovery Rate**
  - c212-package, [3](#)
- \* **Familywise error rate**
  - c212.BONF, [24](#)
- \* **Fisher**
  - c212.fisher.test, [30](#)
- \* **GBH**
  - c212-package, [3](#)
  - c212.err.cntrl, [28](#)
  - c212.GBH, [31](#)
- \* **Gelman-Rubin**
  - c212.convergence.diag, [25](#)
  - c212.print.convergence.summary, [58](#)
- \* **Group Benjamini-Hochberg**
  - c212-package, [3](#)
- \* **Hierarchy**
  - c212.1a, [4](#)
  - c212.1a.interim, [7](#)
  - c212.BB, [11](#)
  - c212.BB.interim, [15](#)
  - c212.convergence.diag, [25](#)
  - c212.gen.initial.values, [32](#)
  - c212.global.sim.params, [33](#)
  - c212.hyper.params, [34](#)
  - c212.interim.1a.hier2, [35](#)
  - c212.interim.1a.hier3, [39](#)
  - c212.interim.BB.hier2, [42](#)
  - c212.interim.BB.hier3, [46](#)
  - c212.monitor.samples, [52](#)
  - c212.plot.eot.data, [54](#)
  - c212.plot.interim.data.rd, [55](#)
  - c212.plot.samples, [56](#)
  - c212.pointmass.weights, [57](#)
  - c212.print.convergence.summary, [58](#)
  - c212.print.summary.stats, [59](#)
  - c212.ptheta, [60](#)
  - c212.sim.control.params, [61](#)
  - c212.summary.stats, [63](#)
- \* **Hypothesis**
  - c212.bin.test, [23](#)
- \* **Interim analysis**
  - c212-package, [3](#)
- \* **Point-mass**
  - c212.BB, [11](#)
  - c212.BB.interim, [15](#)
  - c212.interim.BB.hier2, [42](#)
  - c212.interim.BB.hier3, [46](#)
- \* **Poisson MLE**
  - c212.interim.MLE, [50](#)
- \* **Proportion**
  - c212.bin.test, [23](#)
- \* **Subset Benjamin-Hochberg**
  - c212-package, [3](#)
- \* **Subset Benjamini-Hochberg**
  - c212.ssBH, [62](#)
- \* **System organ class**
  - c212-package, [3](#)
- \* **Test**
  - c212.bin.test, [23](#)
  - c212.fisher.test, [30](#)
- \* **Unadjusted testing**
  - c212.NOADJ, [53](#)
- \* **c212-package**
  - c212-package, [3](#)
- \* **c212.1a.interim**
  - c212.1a.interim, [7](#)
- \* **c212.1a**
  - c212.1a, [4](#)
- \* **c212.BB.interim**
  - c212.BB.interim, [15](#)
- \* **c212.BB**
  - c212.BB, [11](#)
- \* **c212.BH.adjust.pvals**
  - c212.BH.adjust.pvals, [21](#)
- \* **c212.BH**
  - c212.BH, [19](#)
- \* **c212.BONF**
  - c212.BONF, [24](#)
- \* **c212.DFDR**
  - c212.DFDR, [27](#)
- \* **c212.GBH**
  - c212.GBH, [31](#)
- \* **c212.LSL**
  - c212.LSL, [51](#)
- \* **c212.NOADJ**
  - c212.NOADJ, [53](#)
- \* **c212.TST**
  - c212.TST, [66](#)
- \* **c212.bin.test**
  - c212.bin.test, [23](#)
- \* **c212.convergence.diag**
  - c212.convergence.diag, [25](#)
- \* **c212.err.cntrl**
  - c212.err.cntrl, [28](#)
- \* **c212.fisher.test**

- c212.fisher.test, 30
- \* **c212.gen.initial.values**
  - c212.gen.initial.values, 32
- \* **c212.global.sim.params**
  - c212.global.sim.params, 33
- \* **c212.hyper.params**
  - c212.hyper.params, 34
- \* **c212.interim.1a.hier2**
  - c212.interim.1a.hier2, 35
- \* **c212.interim.1a.hier3**
  - c212.interim.1a.hier3, 39
- \* **c212.interim.BB.hier2**
  - c212.interim.BB.hier2, 42
- \* **c212.interim.BB.hier3**
  - c212.interim.BB.hier3, 46
- \* **c212.interim.MLE**
  - c212.interim.MLE, 50
- \* **c212.monitor.samples**
  - c212.monitor.samples, 52
- \* **c212.plot.eot.data**
  - c212.plot.eot.data, 54
- \* **c212.plot.interim.data**
  - c212.plot.interim.data.rd, 55
- \* **c212.plot.samples**
  - c212.plot.samples, 56
- \* **c212.pointmass.weights**
  - c212.pointmass.weights, 57
- \* **c212.print.convergence.summary**
  - c212.print.convergence.summary, 58
- \* **c212.print.summary.stats**
  - c212.print.summary.stats, 59
- \* **c212.ptheta**
  - c212.ptheta, 60
- \* **c212.sim.control.params**
  - c212.sim.control.params, 61
- \* **c212.ssBH**
  - c212.ssBH, 62
- \* **c212.summary.stats**
  - c212.summary.stats, 63
- \* **datasets**
  - c212.FDR.data, 29
  - c212.trial.data, 64
  - c212.trial.interval.data1, 65
  - c212.trial.interval.data2, 65
- \* **ssBH**
  - c212-package, 3
  - c212.err.cntrl, 28
  - c212.ssBH, 62
- c212-package, 3
- c212.1a, 4
- c212.1a.interim, 7
- c212.BB, 11
- c212.BB.interim, 15
- c212.BH, 19
- c212.BH.adjust.pvals, 21
- c212.bin.test, 23
- c212.BONF, 24
- c212.convergence.diag, 25
- c212.DFDR, 27
- c212.err.cntrl, 28
- c212.FDR.data, 29
- c212.fisher.test, 30
- c212.GBH, 31
- c212.gen.initial.values, 32
- c212.global.sim.params, 33
- c212.hyper.params, 34
- c212.interim.1a.hier2, 35
- c212.interim.1a.hier3, 39
- c212.interim.BB.hier2, 42
- c212.interim.BB.hier3, 46
- c212.interim.MLE, 50
- c212.LSL, 51
- c212.monitor.samples, 52
- c212.NOADJ, 53
- c212.plot.eot.data, 54
- c212.plot.interim.data
  - (c212.plot.interim.data.rd), 55
- c212.plot.interim.data.rd, 55
- c212.plot.samples, 56
- c212.pointmass.weights, 57
- c212.print.convergence.summary, 58
- c212.print.summary.stats, 59
- c212.ptheta, 60
- c212.sim.control.params, 61
- c212.ssBH, 62
- c212.summary.stats, 63
- c212.trial.data, 64
- c212.trial.interval.data1, 65
- c212.trial.interval.data2, 65
- c212.TST, 66