Package: rbmi (via r-universe)

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Title Reference Based Multiple Imputation

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Description Implements standard and reference based multiple imputation methods for continuous longitudinal endpoints (Gower-Page et al. (2022) <doi:10.21105/joss.04251>). In particular, this package supports deterministic conditional mean imputation and jackknifing as described in Wolbers et al. (2022) <doi:10.1002/pst.2234>, Bayesian multiple imputation as described in Carpenter et al. (2013) <doi:10.1080/10543406.2013.834911>, and bootstrapped maximum likelihood imputation as described in von Hippel and Bartlett (2021) <doi:10.1214/20-STS793>.

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`adjust_trajectories` *Adjust trajectories due to the intercurrent event (ICE)*

Description

Adjust trajectories due to the intercurrent event (ICE)

Usage

```
adjust_trajectories(
  distr_pars_group,
  outcome,
  ids,
  ind_ice,
  strategy_fun,
  distr_pars_ref = NULL
)
```

Arguments

`distr_pars_group`	Named list containing the simulation parameters of the multivariate normal distribution assumed for the given treatment group. It contains the following elements: • `mu`: Numeric vector indicating the mean outcome trajectory. It should include the outcome at baseline. • `sigma` Covariance matrix of the outcome trajectory.
`outcome`	Numeric variable that specifies the longitudinal outcome.
`ids`	Factor variable that specifies the id of each subject.
`ind_ice`	A binary variable that takes value `1` if the corresponding outcome is affected by the ICE and `0` otherwise.
`strategy_fun`	Function implementing trajectories after the intercurrent event (ICE). Must be one of `getStrategies()`. See `getStrategies()` for details.
`distr_pars_ref`	Optional. Named list containing the simulation parameters of the reference arm. It contains the following elements: • `mu`: Numeric vector indicating the mean outcome trajectory assuming no ICEs. It should include the outcome at baseline. • `sigma` Covariance matrix of the outcome trajectory assuming no ICEs.

Value

A numeric vector containing the adjusted trajectories.

See Also

`adjust_trajectories_single()`.

`adjust_trajectories_single` *Adjust trajectory of a subject's outcome due to the intercurrent event (ICE)*

Description

Adjust trajectory of a subject's outcome due to the intercurrent event (ICE)

Usage

```
adjust_trajectories_single(
  distr_pars_group,
  outcome,
  strategy_fun,
  distr_pars_ref = NULL
)
```

Arguments

`distr_pars_group`	Named list containing the simulation parameters of the multivariate normal distribution assumed for the given treatment group. It contains the following elements: • `mu`: Numeric vector indicating the mean outcome trajectory. It should include the outcome at baseline. • `sigma` Covariance matrix of the outcome trajectory.
`outcome`	Numeric variable that specifies the longitudinal outcome.
`strategy_fun`	Function implementing trajectories after the intercurrent event (ICE). Must be one of `getStrategies()`. See `getStrategies()` for details.
`distr_pars_ref`	Optional. Named list containing the simulation parameters of the reference arm. It contains the following elements: • `mu`: Numeric vector indicating the mean outcome trajectory assuming no ICEs. It should include the outcome at baseline. • `sigma` Covariance matrix of the outcome trajectory assuming no ICEs.

Details

`outcome` should be specified such that all-and-only the post-ICE observations (i.e. the observations to be adjusted) are set to `NA`.

Value

A numeric vector containing the adjusted trajectory for a single subject.

`analyse` *Analyse Multiple Imputed Datasets*

Description

This function takes multiple imputed datasets (as generated by the `impute()` function) and runs an analysis function on each of them.

Usage

```
analyse(
  imputations,
  fun = ancova,
  delta = NULL,
  ...,
  ncores = 1,
  .validate = TRUE
)
```

Arguments

`imputations`	An `imputations` object as created by `impute()`.
`fun`	An analysis function to be applied to each imputed dataset. See details.
`delta`	A `data.frame` containing the delta transformation to be applied to the imputed datasets prior to running `fun`. See details.
`...`	Additional arguments passed onto `fun`.
`ncores`	The number of parallel processes to use when running this function. Can also be a cluster object created by `make_rbmi_cluster()`. See the parallelisation section below.
`.validate`	Should `inputations` be checked to ensure it conforms to the required format (default = `TRUE`) ? Can gain a small performance increase if this is set to `FALSE` when analysing a large number of samples.

Details

This function works by performing the following steps:

1. Extract a dataset from the `imputations` object.
2. Apply any delta adjustments as specified by the `delta` argument.
3. Run the analysis function `fun` on the dataset.
4. Repeat steps 1-3 across all of the datasets inside the `imputations` object.
5. Collect and return all of the analysis results.

The analysis function fun must take a data.frame as its first argument. All other options to analyse() are passed onto fun via .... fun must return a named list with each element itself being a list containing a single numeric element called est (or additionally se and df if you had originally specified method_bayes() or method_approxbayes()) i.e.:

```
myfun <- function(dat, ...) {
    mod_1 <- lm(data = dat, outcome ~ group)
    mod_2 <- lm(data = dat, outcome ~ group + covar)
    x <- list(
        trt_1 = list(
            est = coef(mod_1)[[group]],
            se = sqrt(vcov(mod_1)[group, group]),
            df = df.residual(mod_1)
        ),
        trt_2 = list(
            est = coef(mod_2)[[group]],
            se = sqrt(vcov(mod_2)[group, group]),
            df = df.residual(mod_2)
        )
    )
    return(x)
}
```

Please note that the vars$subjid column (as defined in the original call to draws()) will be scrambled in the data.frames that are provided to fun. This is to say they will not contain the original subject values and as such any hard coding of subject ids is strictly to be avoided.

By default fun is the ancova() function. Please note that this function requires that a vars object, as created by set_vars(), is provided via the vars argument e.g. analyse(imputeObj, vars = set_vars(...)). Please see the documentation for ancova() for full details. Please also note that the theoretical justification for the conditional mean imputation method (method = method_condmean() in draws()) relies on the fact that ANCOVA is a linear transformation of the outcomes. Thus care is required when applying alternative analysis functions in this setting.

Note that ancova() supports the analysis of two or more treatment arms; for more than two arms it extends the ref / alt naming scheme with alt2, alt3, etc. The set of treatment-group contrasts to estimate can be customised via the group_contrasts argument of set_vars(). See ancova() for full details.

The delta argument can be used to specify offsets to be applied to the outcome variable in the imputed datasets prior to the analysis. This is typically used for sensitivity or tipping point analyses. The delta dataset must contain columns vars$subjid, vars$visit (as specified in the original call to draws()) and delta. Essentially this data.frame is merged onto the imputed dataset by vars$subjid and vars$visit and then the outcome variable is modified by:

```
imputed_data[[vars$outcome]] <- imputed_data[[vars$outcome]] + imputed_data[["delta"]]
```

Please note that in order to provide maximum flexibility, the delta argument can be used to modify any/all outcome values including those that were not imputed. Care must be taken when defining offsets. It is recommend that you use the helper function delta_template() to define the delta datasets as this provides utility variables such as is_missing which can be used to identify exactly which visits have been imputed.

Value

An `analysis` object; a list of class `"analysis"` containing the analysis `results` (one entry per imputed dataset, each a named list of parameter estimates), the name of the analysis function (`fun_name`), the applied `delta` data.frame, the analysis function (`fun`) and the imputation `method`. This object is normally passed on to `pool()`.

Parallelisation

To speed up the evaluation of `analyse()` you can use the `ncores` argument to enable parallelisation. Simply providing an integer will get `rbmi` to automatically spawn that many background processes to parallelise across. If you are using a custom analysis function then you need to ensure that any libraries or global objects required by your function are available in the sub-processes. To do this you need to use the `make_rbmi_cluster()` function for example:

```
my_custom_fun <- function(...) <some analysis code>
cl <- make_rbmi_cluster(
    4,
    objects = list("my_custom_fun" = my_custom_fun),
    packages = c("dplyr", "nlme")
)
analyse(
    imputations = imputeObj,
    fun = my_custom_fun,
    ncores = cl
)
parallel::stopCluster(cl)
```

Note that there is significant overhead both with setting up the sub-processes and with transferring data back-and-forth between the main process and the sub-processes. As such parallelisation of the `analyse()` function tends to only be worth it when you have `> 2000` samples generated by `draws()`. Conversely using parallelisation if your samples are smaller than this may lead to longer run times than just running it sequentially.

It is important to note that the implementation of parallel processing within `analyse()` has been optimised around the assumption that the parallel processes will be spawned on the same machine and not a remote cluster. One such optimisation is that the required data is saved to a temporary file on the local disk from which it is then read into each sub-process. This is done to avoid the overhead of transferring the data over the network. Our assumption is that if you are at the stage where you need to be parallelising your analysis over a remote cluster then you would likely be better off parallelising across multiple `rbmi` runs rather than within a single `rbmi` run.

Finally, if you are doing a tipping point analysis you can get a reasonable performance improvement by re-using the cluster between each call to `analyse()` e.g.

```
cl <- make_rbmi_cluster(4)
ana_1 <- analyse(
    imputations = imputeObj,
    delta = delta_plan_1,
    ncores = cl
```

```
)
ana_2 <- analyse(
    imputations = imputeObj,
    delta = delta_plan_2,
    ncores = cl
)
ana_3 <- analyse(
    imputations = imputeObj,
    delta = delta_plan_3,
    ncores = cl
)
parallel::clusterStop(cl)
```

See Also

extract_imputed_dfs() for manually extracting imputed datasets.

delta_template() for creating delta data.frames.

ancova() for the default analysis function.

Examples

```
## Not run:
vars <- set_vars(
    subjid = "subjid",
    visit = "visit",
    outcome = "outcome",
    group = "group",
    covariates = c("sex", "age", "sex*age")
)

analyse(
    imputations = imputeObj,
    vars = vars
)

deltadf <- data.frame(
    subjid = c("Pt1", "Pt1", "Pt2"),
    visit = c("Visit_1", "Visit_2", "Visit_2"),
    delta = c( 5, 9, -10)
)

analyse(
    imputations = imputeObj,
    delta = deltadf,
    vars = vars
)

## End(Not run)
```

ancova *Analysis of Covariance*

Description

Performs an analysis of covariance between two or more treatment groups returning the estimated "treatment effect" (i.e. the contrast between treatment groups) and the least square means estimates in each group.

Usage

```
ancova(
  data,
  vars,
  visits = NULL,
  weights = c("counterfactual", "equal", "proportional_em", "proportional")
)
```

Arguments

`data`	A `data.frame` containing the data to be used in the model.
`vars`	A `vars` object as generated by `set_vars()`. Only the `group`, `visit`, `outcome` and `covariates` elements are required. See details.
`visits`	An optional character vector specifying which visits to fit the ANCOVA model at. If `NULL`, a separate ANCOVA model will be fit to the outcomes for each visit (as determined by `unique(data[[vars$visit]])`). See details.
`weights`	Character, either `"counterfactual"` (default), `"equal"`, `"proportional_em"` or `"proportional"`. Specifies the weighting strategy to be used when calculating the lsmeans. See the weighting section for more details.

Details

The function works as follows:

1. Select the first value from `visits`.
2. Subset the data to only the observations that occurred on this visit.
3. Fit a linear model as `vars$outcome ~ vars$group + vars$covariates`.
4. Extract the "treatment effect" & least square means for each treatment group.
5. Repeat points 2-3 for all other values in `visits`.

If no value for `visits` is provided then it will be set to `unique(data[[vars$visit]])`.

In order to meet the formatting standards set by `analyse()` the results will be collapsed into a single list suffixed by the visit name, e.g.:

```
list(
   trt_visit_1 = list(est = ...),
   lsm_ref_visit_1 = list(est = ...),
   lsm_alt_visit_1 = list(est = ...),
   trt_visit_2 = list(est = ...),
   lsm_ref_visit_2 = list(est = ...),
   lsm_alt_visit_2 = list(est = ...),
   ...
)
```

ancova() supports two or more treatment groups. The group levels are referred to via a fixed naming scheme derived from the factor levels of vars$group: ref is the first factor level, alt the second, alt2 the third, alt3 the fourth, and so on. Note that ref does not necessarily coincide with the control arm; it is simply the first factor level.

The least square means for each group are returned as lsm_ref, lsm_alt, lsm_alt2, etc. Treatment effects (model contrasts) are returned as trt for the alt vs ref comparison, trt_alt2 for alt2 vs ref, and so on. For the common case of two groups this reduces to the original trt, lsm_ref and lsm_alt naming, ensuring backwards compatibility.

By default a treatment effect is calculated for every non-reference group versus the reference group, using the trt / trt_alt2 / ... names described above. Alternatively a bespoke set of contrasts can be requested via the group_contrasts argument of set_vars(); see its documentation for details. Such contrasts must be named, and the supplied name is used as the parameter name and carried through to the contrast_label column of the pool() output. Contrasts may be pairwise (a length-2 c(minuend, subtrahend) character vector) or general linear contrasts (a named numeric weight vector over the group levels).

If you want to include interaction terms in your model this can be done by providing them to the covariates argument of set_vars() e.g. set_vars(covariates = c("sex*age")). Interactions involving the treatment group (vars$group) are not supported and will result in an error, because the treatment contrasts would depend on the reference values of the interacting covariates.

Note that the treatment effects (trt, trt_alt2, ...) are the relevant linear combinations of the group main-effect coefficients. The least square means (lsm_*) are computed according to the requested weights.

For treatment contrasts, numeric covariates are set to their observed means within each visit, excluding missing values, before formula transformations are applied (e.g. log(mean(age, na.rm = TRUE)) for log(age)). Factor covariates are set to their first level and logical covariates to FALSE. With treatment-group interactions excluded, these reference values do not affect the treatment contrasts, provided the transformed values are finite.

Value

A named list with one set of entries per visit, each suffixed by the visit name. For each visit the list contains:

- the estimated treatment effect(s). For the default (group_contrasts = NULL) these are trt_<visit> for the alt vs ref comparison and trt_alt2_<visit>, trt_alt3_<visit>, ... for further non-reference groups versus the reference group. When group_contrasts is supplied each contrast is named <name>_<visit> using the list name given for that contrast. Also

- the least square means for each group (`lsm_ref_<visit>`, `lsm_alt_<visit>`, `lsm_alt2_<visit>`, ...).

For the common case of two groups this reduces to `trt_<visit>`, `lsm_ref_<visit>` and `lsm_alt_<visit>`. Each of these elements is itself a list holding the estimate (`est`), standard error (`se`) and degrees of freedom (`df`).

Weighting

Counterfactual:

For `weights = "counterfactual"` (the default) the lsmeans are obtained by taking the average of the predicted values for each patient after assigning all patients to each arm in turn. This approach is equivalent to standardization or g-computation. In comparison to `emmeans` this approach is equivalent to:

```
emmeans::emmeans(model, specs = "<treatment>", counterfactual = "<treatment>")
```

Note that to ensure backwards compatibility with previous versions of `rbmi` `weights = "proportional"` is an alias for `weights = "counterfactual"`. To get results consistent with `emmeans`'s `weights = "proportional"` please use `weights = "proportional_em"`.

Equal:

For `weights = "equal"` the lsmeans are obtained by taking the model fitted value of a hypothetical patient whose covariates are defined as follows:

- Continuous covariates are set to `mean(X)`
- Dummy categorical variables are set to `1/N` where `N` is the number of levels
- Continuous * continuous interactions are set to `mean(X) * mean(Y)`
- Continuous * categorical interactions are set to `mean(X) * 1/N`
- Dummy categorical * categorical interactions are set to `1/N * 1/M`

In comparison to `emmeans` this approach is equivalent to:

```
emmeans::emmeans(model, specs = "<treatment>", weights = "equal")
```

Proportional:

For `weights = "proportional_em"` the lsmeans are obtained as per `weights = "equal"` except instead of weighting each observation equally they are weighted by the proportion in which the given combination of categorical values occurred in the data. In comparison to `emmeans` this approach is equivalent to:

```
emmeans::emmeans(model, specs = "<treatment>", weights = "proportional")
```

Note that this is not to be confused with `weights = "proportional"` which is an alias for `weights = "counterfactual"`.

See Also

`analyse()`

`stats::lm()`

`set_vars()`

Examples

```
# Simulate a small dataset with a single visit, a treatment group and a
# baseline covariate to adjust for.
set.seed(101)
dat <- data.frame(
    visit = factor("visit_1"),
    group = factor(rep(c("Control", "Intervention"), each = 50)),
    basval = rnorm(100)
)
dat$outcome <- 5 + 2 * (dat$group == "Intervention") + dat$basval + rnorm(100)

vars <- set_vars(
    outcome = "outcome",
    group = "group",
    visit = "visit",
    covariates = "basval"
)

# Estimated treatment effect and least square means for the single visit.
# In a full `rbmi` analysis, `ancova()` is passed to `analyse()` rather than
# called directly; see [analyse()].
ancova(dat, vars)

# Multi-arm ANCOVA with a bespoke, named set of contrasts. With three groups
# the default would compare each active arm against the reference ("Placebo");
# here we additionally request the "High" vs "Low" contrast. Explicit contrasts
# must be named, and the names become the output parameter names.
set.seed(102)
dat3 <- data.frame(
    visit = factor("visit_1"),
    group = factor(
        rep(c("Placebo", "Low", "High"), each = 50),
        levels = c("Placebo", "Low", "High")
    ),
    basval = rnorm(150)
)
dat3$outcome <- 5 +
    2 * (dat3$group == "Low") +
    4 * (dat3$group == "High") +
    dat3$basval +
    rnorm(150)

vars3 <- set_vars(
    outcome = "outcome",
    group = "group",
    visit = "visit",
    covariates = "basval",
    group_contrasts = list(
        low_vs_pbo  = c("Low", "Placebo"),
        high_vs_pbo = c("High", "Placebo"),
        high_vs_low = c("High", "Low")
    )
```

```
)

# Output names: `low_vs_pbo`, `high_vs_pbo`, `high_vs_low`, plus
# `lsm_ref` / `lsm_alt` / `lsm_alt2`.
names(ancova(dat3, vars3))
```

`antidepressant_data` *Antidepressant trial data*

Description

A dataset containing data from a publicly available example data set from an antidepressant clinical trial. The dataset is available on the website of the Drug Information Association Scientific Working Group on Estimands and Missing Data. As per that website, the original data are from an antidepressant clinical trial with four treatments; two doses of an experimental medication, a positive control, and placebo and was published in Goldstein et al (2004). To mask the real data, week 8 observations were removed and two arms were created: the original placebo arm and a "drug arm" created by randomly selecting patients from the three non-placebo arms.

Usage

```
antidepressant_data
```

Format

A `data.frame` with 608 rows and 11 variables:

- `PATIENT`: patients IDs.
- `HAMATOTL`: total score Hamilton Anxiety Rating Scale.
- `PGIIMP`: patient's Global Impression of Improvement Rating Scale.
- `RELDAYS`: number of days between visit and baseline.
- `VISIT`: post-baseline visit. Has levels 4,5,6,7.
- `THERAPY`: the treatment group variable. It is equal to `PLACEBO` for observations from the placebo arm, or `DRUG` for observations from the active arm.
- `GENDER`: patient's gender.
- `POOLINV`: pooled investigator.
- `BASVAL`: baseline outcome value.
- `HAMDTL17`: Hamilton 17-item rating scale value.
- `CHANGE`: change from baseline in the Hamilton 17-item rating scale.

Details

The relevant endpoint is the Hamilton 17-item rating scale for depression (HAMD17) for which baseline and weeks 1, 2, 4, and 6 assessments are included. Study drug discontinuation occurred in 24% subjects from the active drug and 26% from placebo. All data after study drug discontinuation are missing and there is a single additional intermittent missing observation.

References

Goldstein, Lu, Detke, Wiltse, Mallinckrodt, Demitrack. Duloxetine in the treatment of depression: a double-blind placebo-controlled comparison with paroxetine. J Clin Psychopharmacol 2004;24: 389-399.

`apply_delta` *Applies delta adjustment*

Description

Takes a delta dataset and adjusts the outcome variable by adding the corresponding delta.

Usage

```
apply_delta(data, delta = NULL, group = NULL, outcome = NULL)
```

Arguments

`data`	`data.frame` which will have its `outcome` column adjusted.
`delta`	`data.frame` (must contain a column called `delta`).
`group`	character vector of variables in both `data` and `delta` that will be used to merge the 2 data.frames together by.
`outcome`	character, name of the outcome variable in `data`.

`as_analysis` *Construct an* `analysis` *object*

Description

Creates an analysis object ensuring that all components are correctly defined.

Usage

```
as_analysis(
  results,
  method,
  delta = NULL,
  fun = NULL,
  fun_name = NULL,
  par_meta = NULL
)
```

Arguments

results	A list of lists contain the analysis results for each imputation See analyse() for details on what this object should look like.
method	The method object as specified in draws().
delta	The delta dataset used. See analyse() for details on how this should be specified.
fun	The analysis function that was used.
fun_name	The character name of the analysis function (used for printing) purposes.
par_meta	Optional data.frame of per-parameter metadata (e.g. the group levels and visit associated with each analysis parameter) as attached by the analysis function. May be NULL.

---

as_ascii_table *as_ascii_table*

Description

This function takes a data.frame and attempts to convert it into a simple ascii format suitable for printing to the screen It is assumed all variable values have a as.character() method in order to cast them to character.

Usage

```
as_ascii_table(dat, line_prefix = "  ", pcol = NULL)
```

Arguments

dat	Input dataset to convert into a ascii table
line_prefix	Symbols to prefix in front of every line of the table
pcol	name of column to be handled as a p-value. Sets the value to <0.001 if the value is 0 after rounding

---

as_cropped_char *as_cropped_char*

Description

Makes any character string above x chars Reduce down to a x char string with ...

Usage

```
as_cropped_char(inval, crop_at = 30, ndp = 3)
```

Arguments

inval	a single element value
crop_at	character limit
ndp	Number of decimal places to display

---

as_dataframe *Convert object to dataframe*

Description

Convert object to dataframe

Usage

```
as_dataframe(x)
```

Arguments

x	a data.frame like object Utility function to convert a "data.frame-like" object to an actual data.frame to avoid issues with inconsistency on methods (such as [() and dplyr's grouped dataframes)

---

as_draws *Creates a* draws *object*

Description

Creates a draws object which is the final output of a call to draws().

Usage

```
as_draws(method, samples, data, formula, n_failures = NULL, fit = NULL)
```

Arguments

method	A method object as generated by either method_bayes(), method_approxbayes(), method_condmean() or method_bmlmi().
samples	A list of sample_single objects. See sample_single().
data	R6 longdata object containing all relevant input data information.
formula	Fixed effects formula object used for the model specification.
n_failures	Absolute number of failures of the model fit.
fit	If method_bayes() is chosen, returns the MCMC Stan fit object. Otherwise NULL.

Value

A draws object which is a named list containing the following:

- data: R6 longdata object containing all relevant input data information.
- method: A method object as generated by either method_bayes(), method_approxbayes() or method_condmean().
- samples: list containing the estimated parameters of interest. Each element of samples is a named list containing the following:
  - ids: vector of characters containing the ids of the subjects included in the original dataset.
  - beta: numeric vector of estimated regression coefficients.
  - sigma: list of estimated covariance matrices (one for each level of vars$group).
  - theta: numeric vector of transformed covariances.
  - failed: Logical. TRUE if the model fit failed.
  - ids_samp: vector of characters containing the ids of the subjects included in the given sample.
- fit: if method_bayes() is chosen, returns the MCMC Stan fit object. Otherwise NULL.
- n_failures: absolute number of failures of the model fit. Relevant only for method_condmean(type = "bootstrap"), method_approxbayes() and method_bmlmi().
- formula: fixed effects formula object used for the model specification.

---

as_imputation *Create an imputation object*

Description

This function creates the object that is returned from impute(). Essentially it is a glorified wrapper around list() ensuring that the required elements have been set and that the class is added as expected.

Usage

```
as_imputation(imputations, data, method, references)
```

Arguments

imputations	A list of imputations_list's as created by imputation_df()
data	A longdata object as created by longDataConstructor()
method	A method object as created by method_condmean(), method_bayes() or method_approxbayes()
references	A named vector. Identifies the references to be used when generating the imputed values. Should be of the form c("Group" = "Reference", "Group" = "Reference").

as_indices *Convert indicator to index*

Description

Converts a string of 0's and 1's into index positions of the 1's padding the results by 0's so they are all the same length

Usage

```
as_indices(x)
```

Arguments

x	a character vector whose values are all either "0" or "1". All elements of the vector must be the same length

Details

i.e.

```
patmap(c("1101", "0001"))  ->  list(c(1,2,4,999), c(4,999, 999, 999))
```

as_mmrm_df *Creates a "MMRM" ready dataset*

Description

Converts a design matrix + key variables into a common format In particular this function does the following:

- Renames all covariates as `V1`, `V2`, etc to avoid issues of special characters in variable names
- Ensures all key variables are of the right type
- Inserts the `outcome`, `visit` and `subjid` variables into the `data.frame` naming them as `outcome`, `visit` and `subjid`
- If provided will also insert the group variable into the `data.frame` named as `group`

Usage

```
as_mmrm_df(designmat, outcome, visit, subjid, group = NULL)
```

Arguments

designmat	a data.frame or matrix containing the covariates to use in the MMRM model. Dummy variables must already be expanded out, i.e. via stats::model.matrix(). Cannot contain any missing values
outcome	a numeric vector. The outcome value to be regressed on in the MMRM model.
visit	a character / factor vector. Indicates which visit the outcome value occurred on.
subjid	a character / factor vector. The subject identifier used to link separate visits that belong to the same subject.
group	a character / factor vector. Indicates which treatment group the patient belongs to. Will internally be converted to a factor if it is a character vector.

---

as_mmrm_formula *Create MMRM formula*

Description

Derives the MMRM model formula from the structure of mmrm_df. returns a formula object of the form:

Usage

```
as_mmrm_formula(mmrm_df, cov_struct)
```

Arguments

mmrm_df	an mmrm data.frame as created by as_mmrm_df()
cov_struct	Character - The covariance structure to be used, must be one of "us" (default), "ad", "adh", "ar1", "ar1h", "cs", "csh", "toep", or "toeph")

Details

```
outcome ~ 0 + V1 + V2 + V4 + ... + us(visit | group / subjid)
```

---

as_model_df *Expand* data.frame *into a design matrix*

Description

Expands out a data.frame using a formula to create a design matrix. Key details are that it will always place the outcome variable into the first column of the return object.

Usage

```
as_model_df(dat, frm)
```

Arguments

dat	a data.frame
frm	a formula

Details

The outcome column may contain NA, but none of the other variables listed in the formula should contain missing values

---

as_simple_formula *Creates a simple formula object from a string*

Description

Converts a string list of variables into a formula object

Usage

```
as_simple_formula(outcome, covars)
```

Arguments

outcome	character (length 1 vector). Name of the outcome variable
covars	character (vector). Name of covariates

Value

A formula

---

as_stan_array *As array*

Description

Converts a numeric value of length 1 into a 1 dimension array. This is to avoid type errors that are thrown by Stan when length 1 numeric vectors are provided by R for `stan::vector` inputs

Usage

```
as_stan_array(x)
```

Arguments

x	a numeric vector

as_strata *Create vector of strata*

Description

Collapse multiple categorical variables into distinct unique categories. e.g.

```
as_strata(c(1,1,2,2,2,1), c(5,6,5,5,6,5))
```

would return

```
c(1,2,3,3,4,1)
```

Usage

```
as_strata(...)
```

Arguments

...	numeric/character/factor vectors of the same length

Examples

```
## Not run:
as_strata(c(1,1,2,2,2,1), c(5,6,5,5,6,5))

## End(Not run)
```

assert_variables_exist *Assert that all variables exist within a dataset*

Description

Performs an assertion check to ensure that a vector of variable exists within a data.frame as expected.

Usage

```
assert_variables_exist(data, vars)
```

Arguments

data	a data.frame
vars	a character vector of variable names

char2fct *Convert character variables to factor*

Description

Provided a vector of variable names this function converts any character variables into factors. Has no affect on numeric or existing factor variables

Usage

```
char2fct(data, vars = NULL)
```

Arguments

data	A data.frame
vars	a character vector of variables in data

check_ESS *Diagnostics of the MCMC based on ESS*

Description

Check the quality of the MCMC draws from the posterior distribution by checking whether the relative ESS is sufficiently large.

Usage

```
check_ESS(stan_fit, n_draws, threshold_lowESS = 0.4)
```

Arguments

stan_fit	A stanfit object.
n_draws	Number of MCMC draws.
threshold_lowESS	A number in [0,1] indicating the minimum acceptable value of the relative ESS. See details.

Details

check_ESS() works as follows:

1. Extract the ESS from stan_fit for each parameter of the model.
2. Compute the relative ESS (i.e. the ESS divided by the number of draws).
3. Check whether for any of the parameter the ESS is lower than threshold. If for at least one parameter the relative ESS is below the threshold, a warning is thrown.

Value

A warning message in case of detected problems.

`check_hmc_diagn` *Diagnostics of the MCMC based on HMC-related measures.*

Description

Check that:

1. There are no divergent iterations.
2. The Bayesian Fraction of Missing Information (BFMI) is sufficiently low.
3. The number of iterations that saturated the max treedepth is zero.

Please see `rstan::check_hmc_diagnostics()` for details.

Usage

```
check_hmc_diagn(stan_fit)
```

Arguments

`stan_fit`	A `stanfit` object.

Value

A warning message in case of detected problems.

`check_mcmc` *Diagnostics of the MCMC*

Description

Diagnostics of the MCMC

Usage

```
check_mcmc(stan_fit, n_draws, threshold_lowESS = 0.4)
```

Arguments

`stan_fit`	A `stanfit` object.
`n_draws`	Number of MCMC draws.
`threshold_lowESS`	A number in `[0,1]` indicating the minimum acceptable value of the relative ESS. See details.

Details

Performs checks of the quality of the MCMC. See `check_ESS()` and `check_hmc_diagn()` for details.

Value

A warning message in case of detected problems.

`compute_sigma` *Compute covariance matrix for some reference-based methods (JR, CIR)*

Description

Adapt covariance matrix in reference-based methods. Used for Copy Increments in Reference (CIR) and Jump To Reference (JTR) methods, to adapt the covariance matrix to different pre-deviation and post deviation covariance structures. See Carpenter et al. (2013)

Usage

```
compute_sigma(sigma_group, sigma_ref, index_mar)
```

Arguments

`sigma_group`	the covariance matrix with dimensions equal to `index_mar` for the subjects original group
`sigma_ref`	the covariance matrix with dimensions equal to `index_mar` for the subjects reference group
`index_mar`	A logical vector indicating which visits meet the MAR assumption for the subject. I.e. this identifies the observations that after a non-MAR intercurrent event (ICE).

References

Carpenter, James R., James H. Roger, and Michael G. Kenward. "Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation." Journal of Biopharmaceutical statistics 23.6 (2013): 1352-1371.

control *Control the computational details of the imputation methods*

Description

These functions control lower level computational details of the imputation methods.

Usage

```
control_bayes(
  warmup = 200,
  thin = 50,
  chains = 1,
  init = ifelse(chains > 1, "random", "mmrm"),
  seed = sample.int(.Machine$integer.max, 1),
  ...
)
```

Arguments

warmup	a numeric, the number of warmup iterations for the MCMC sampler.
thin	a numeric, the thinning rate of the MCMC sampler.
chains	a numeric, the number of chains to run in parallel.
init	a character string, the method used to initialise the MCMC sampler, see the details.
seed	a numeric, the seed used to initialise the MCMC sampler.
...	additional arguments to be passed to rstan::sampling().

Details

Currently only the Bayesian imputation via method_bayes() uses a control function:

- The init argument can be set to "random" to randomly initialise the sampler with rstan default values or to "mmrm" to initialise the sampler with the maximum likelihood estimate values of the MMRM.
- The seed argument is used to set the seed for the MCMC sampler. By default, a random seed is generated, such that outside invocation of the set.seed() call can effectively set the seed.
- The samples are split across the chains, such that each chain produces n_samples / chains (rounded up) samples. The total number of samples that will be returned across all chains is n_samples as specified in method_bayes().
- Therefore, the additional parameters passed to rstan::sampling() must not contain n_samples or iter. Instead, the number of samples must only be provided directly via the n_samples argument of method_bayes(). Similarly, the refresh argument is also not allowed here, instead use the quiet argument directly in draws().

Value

A named list of control parameters (`warmup`, `thin`, `chains`, `init`, `seed` and any additional arguments passed via `...`) that control the MCMC sampler used by `method_bayes()`.

Note

For full reproducibility of the imputation results, it is required to use a `set.seed()` call before defining the `control` list, and calling the `draws()` function. It is not sufficient to merely set the `seed` argument in the `control` list.

Examples

```
# Default control settings
control_bayes()

# Customise the warmup, thinning and seed used by the MCMC sampler
control_bayes(warmup = 200, thin = 5, seed = 1821)

# Pass the control settings on to method_bayes()
method_bayes(
    n_samples = 150,
    control = control_bayes(warmup = 200, thin = 5, seed = 1821)
)
```

---

convert_to_imputation_list_df

Convert list of `imputation_list_single()` objects to an `imputation_list_df()` object (i.e. a list of `imputation_df()` objects)

Description

Convert list of `imputation_list_single()` objects to an `imputation_list_df()` object (i.e. a list of `imputation_df()` objects)

Usage

```
convert_to_imputation_list_df(imputes, sample_ids)
```

Arguments

`imputes`	a list of `imputation_list_single()` objects
`sample_ids`	A list with 1 element per required `imputation_df`. Each element must contain a vector of "ID"'s which correspond to the `imputation_single()` ID's that are required for that dataset. The total number of ID's must by equal to the total number of rows within all of `imputes$imputations`

To accommodate for method_bmlmi() the impute_data_individual() function returns a list of imputation_list_single() objects with 1 object per each subject.

imputation_list_single() stores the subjects imputations as a matrix where the columns of the matrix correspond to the D of method_bmlmi(). Note that all other methods (i.e. methods_*()) are a special case of this with D = 1. The number of rows in the matrix varies for each subject and is equal to the number of times the patient was selected for imputation (for non-conditional mean methods this should be 1 per subject per imputed dataset).

This function is best illustrated by an example:

```
imputes = list(
    imputation_list_single(
        id = "Tom",
        imputations = matrix(
             imputation_single_t_1_1,  imputation_single_t_1_2,
             imputation_single_t_2_1,  imputation_single_t_2_2,
             imputation_single_t_3_1,  imputation_single_t_3_2
        )
    ),
    imputation_list_single(
        id = "Tom",
        imputations = matrix(
             imputation_single_h_1_1,  imputation_single_h_1_2,
        )
    )
)

sample_ids <- list(
    c("Tom", "Harry", "Tom"),
    c("Tom")
)
```

Then convert_to_imputation_df(imputes, sample_ids) would result in:

```
imputation_list_df(
    imputation_df(
        imputation_single_t_1_1,
        imputation_single_h_1_1,
        imputation_single_t_2_1
    ),
    imputation_df(
        imputation_single_t_1_2,
        imputation_single_h_1_2,
        imputation_single_t_2_2
    ),
    imputation_df(
        imputation_single_t_3_1
    ),
```

```
    imputation_df(
        imputation_single_t_3_2
    )
)
```

Note that the different repetitions (i.e. the value set for D) are grouped together sequentially.

`d_lagscale` *Calculate delta from a lagged scale coefficient*

Description

Calculates a delta value based upon a baseline delta value and a post ICE scaling coefficient.

Usage

```
d_lagscale(delta, dlag, is_post_ice)
```

Arguments

`delta`	a numeric vector. Determines the baseline amount of delta to be applied to each visit.
`dlag`	a numeric vector. Determines the scaling to be applied to `delta` based upon with visit the ICE occurred on. Must be the same length as delta.
`is_post_ice`	logical vector. Indicates whether a visit is "post-ICE" or not.

Details

See `delta_template()` for full details on how this calculation is performed.

`delta_template` *Create a delta* `data.frame` *template*

Description

Creates a `data.frame` in the format required by `analyse()` for the use of applying a delta adjustment.

Usage

```
delta_template(imputations, delta = NULL, dlag = NULL, missing_only = TRUE)
```

Arguments

imputations	an imputation object as created by impute().
delta	NULL or a numeric vector. Determines the baseline amount of delta to be applied to each visit. See details. If a numeric vector it must have the same length as the number of unique visits in the original dataset.
dlag	NULL or a numeric vector. Determines the scaling to be applied to delta based upon which visit the ICE occurred on. See details. If a numeric vector it must have the same length as the number of unique visits in the original dataset.
missing_only	Logical, if TRUE then non-missing post-ICE data will have a delta value of 0 assigned. Note that the calculation (as described in the details section) is performed first and then overwritten with 0's at the end (i.e. the delta values for missing post-ICE visits will stay the same regardless of this option).

Details

To apply a delta adjustment the analyse() function expects a delta data.frame with 3 variables: vars$subjid, vars$visit and delta (where vars is the object supplied in the original call to draws() as created by the set_vars() function).

This function will return a data.frame with the aforementioned variables with one row per subject per visit. If the delta argument to this function is NULL then the delta column in the returned data.frame will be 0 for all observations. If the delta argument is not NULL then delta will be calculated separately for each subject as the accumulative sum of delta multiplied by the scaling coefficient dlag based upon how many visits after the subject's intercurrent event (ICE) the visit in question is. This is best illustrated with an example:

Let delta = c(5,6,7,8) and dlag=c(1,2,3,4) (i.e. assuming there are 4 visits) and lets say that the subject had an ICE on visit 2. The calculation would then be as follows:

```
v1  v2  v3  v4
--------------
 5   6   7   8  # delta assigned to each visit
 0   1   2   3  # lagged scaling starting from the first visit after the subjects ICE
--------------
 0   6  14  24  # delta * lagged scaling
--------------
 0   6  20  44  # accumulative sum of delta to be applied to each visit
```

That is to say the subject would have a delta offset of 0 applied for visit-1, 6 for visit-2, 20 for visit-3 and 44 for visit-4. As a comparison, lets say that the subject instead had their ICE on visit 3, the calculation would then be as follows:

```
v1  v2  v3  v4
--------------
 5   6   7   8  # delta assigned to each visit
 0   0   1   2  # lagged scaling starting from the first visit after the subjects ICE
--------------
 0   0   7  16  # delta * lagged scaling
--------------
 0   0   7  23  # accumulative sum of delta to be applied to each visit
```

In terms of practical usage, lets say that you wanted a delta of 5 to be used for all post ICE visits regardless of their proximity to the ICE visit. This can be achieved by setting `delta = c(5,5,5,5)` and `dlag = c(1,0,0,0)`. For example lets say a subject had their ICE on visit-1, then the calculation would be as follows:

```
v1  v2  v3  v4
--------------
 5   5   5   5  # delta assigned to each visit
 1   0   0   0 # lagged scaling starting from the first visit after the subjects ICE
--------------
 5   0   0   0  # delta * lagged scaling
--------------
 5   5   5   5  # accumulative sum of delta to be applied to each visit
```

Another way of using these arguments is to set `delta` to be the difference in time between visits and `dlag` to be the amount of delta per unit of time. For example lets say that we have a visit on weeks 1, 5, 6 & 9 and that we want a delta of 3 to be applied for each week after an ICE. This can be achieved by setting `delta = c(0,4,1,3)` (the difference in weeks between each visit) and `dlag = c(3, 3, 3, 3)`. For example lets say we have a subject who had their ICE on week-5 (i.e. visit-2) then the calculation would be:

```
v1  v2  v3  v4
--------------
 0   4   1   3  # delta assigned to each visit
 0   0   3   3 # lagged scaling starting from the first visit after the subjects ICE
--------------
 0   0   3   9  # delta * lagged scaling
--------------
 0   0   3  12  # accumulative sum of delta to be applied to each visit
```

i.e. on week-6 (1 week after the ICE) they have a delta of 3 and on week-9 (4 weeks after the ICE) they have a delta of 12.

Please note that this function also returns several utility variables so that the user can create their own custom logic for defining what `delta` should be set to. These additional variables include:

- `is_mar` - If the observation was missing would it be regarded as MAR? This variable is set to `FALSE` for observations that occurred after a non-MAR ICE, otherwise it is set to `TRUE`.
- `is_missing` - Is the outcome variable for this observation missing.
- `is_post_ice` - Does the observation occur after the patient's ICE as defined by the `data_ice` dataset supplied to `draws()`.
- `strategy` - What imputation strategy was assigned to for this subject.

The design and implementation of this function is largely based upon the same functionality as implemented in the so called "five macros" by James Roger. See Roger (2021).

Value

A data.frame with one row per subject per visit containing the variables vars$subjid, vars$visit and delta (the delta offset to apply), together with the utility variables is_mar, is_missing, is_post_ice and strategy which can be used to define custom delta logic. If delta is NULL the delta column is 0 for all observations.

References

Roger, James. Reference-based MI via Multivariate Normal RM (the "five macros" and MIWithD), 2021. URL https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data.

See Also

analyse()

Examples

```
## Not run:
delta_template(imputeObj)
delta_template(imputeObj, delta = c(5,6,7,8), dlag = c(1,2,3,4))

## End(Not run)
```

---

draws *Fit the base imputation model and get parameter estimates*

Description

draws fits the base imputation model to the observed outcome data according to the given multiple imputation methodology. According to the user's method specification, it returns either draws from the posterior distribution of the model parameters as required for Bayesian multiple imputation or frequentist parameter estimates from the original data and bootstrapped or leave-one-out datasets as required for conditional mean imputation. The purpose of the imputation model is to estimate model parameters in the absence of intercurrent events (ICEs) handled using reference-based imputation methods. For this reason, any observed outcome data after ICEs, for which reference-based imputation methods are specified, are removed and considered as missing for the purpose of estimating the imputation model, and for this purpose only. The imputation model is a mixed model for repeated measures (MMRM) that is valid under a missing-at-random (MAR) assumption. It can be fit using maximum likelihood (ML) or restricted ML (REML) estimation, a Bayesian approach, or an approximate Bayesian approach according to the user's method specification. The ML/REML approaches and the approximate Bayesian approach support several possible covariance structures, while the Bayesian approach based on MCMC sampling supports only an unstructured covariance structure. In any case the covariance matrix can be assumed to be the same or different across each group.

Usage

```
draws(data, data_ice = NULL, vars, method, ncores = 1, quiet = FALSE)

## S3 method for class 'approxbayes'
draws(data, data_ice = NULL, vars, method, ncores = 1, quiet = FALSE)

## S3 method for class 'condmean'
draws(data, data_ice = NULL, vars, method, ncores = 1, quiet = FALSE)

## S3 method for class 'bmlmi'
draws(data, data_ice = NULL, vars, method, ncores = 1, quiet = FALSE)

## S3 method for class 'bayes'
draws(data, data_ice = NULL, vars, method, ncores = 1, quiet = FALSE)
```

Arguments

data	A data.frame containing the data to be used in the model. See details.
data_ice	A data.frame that specifies the information related to the ICEs and the imputation strategies. See details.
vars	A vars object as generated by set_vars(). See details.
method	A method object as generated by either method_bayes(), method_approxbayes(), method_condmean() or method_bmlmi(). It specifies the multiple imputation methodology to be used. See details.
ncores	A single numeric specifying the number of cores to use in creating the draws object. Note that this parameter is ignored for method_bayes() (Default = 1). Can also be a cluster object generated by make_rbmi_cluster()
quiet	Logical, if TRUE will suppress printing of progress information that is printed to the console.

Details

draws performs the first step of the multiple imputation (MI) procedure: fitting the base imputation model. The goal is to estimate the parameters of interest needed for the imputation phase (i.e. the regression coefficients and the covariance matrices from a MMRM model).

The function distinguishes between the following methods:

- Bayesian MI based on MCMC sampling: draws returns the draws from the posterior distribution of the parameters using a Bayesian approach based on MCMC sampling. This method can be specified by using method = method_bayes().
- Approximate Bayesian MI based on bootstrapping: draws returns the draws from the posterior distribution of the parameters using an approximate Bayesian approach, where the sampling from the posterior distribution is simulated by fitting the MMRM model on bootstrap samples of the original dataset. This method can be specified by using method = method_approxbayes()].
- Conditional mean imputation with bootstrap re-sampling: draws returns the MMRM parameter estimates from the original dataset and from n_samples bootstrap samples. This method can be specified by using method = method_condmean() with argument type = "bootstrap".

- Conditional mean imputation with jackknife re-sampling: `draws` returns the MMRM parameter estimates from the original dataset and from each leave-one-subject-out sample. This method can be specified by using `method = method_condmean()` with argument `type = "jackknife"`.
- Bootstrapped Maximum Likelihood MI: `draws` returns the MMRM parameter estimates from a given number of bootstrap samples needed to perform random imputations of the bootstrapped samples. This method can be specified by using `method = method_bmlmi()`.

Bayesian MI based on MCMC sampling has been proposed in Carpenter, Roger, and Kenward (2013) who first introduced reference-based imputation methods. Approximate Bayesian MI is discussed in Little and Rubin (2002). Conditional mean imputation methods are discussed in Wolbers et al (2022). Bootstrapped Maximum Likelihood MI is described in Von Hippel & Bartlett (2021).

The argument `data` contains the longitudinal data. It must have at least the following variables:

- `subjid`: a factor vector containing the subject ids.
- `visit`: a factor vector containing the visit the outcome was observed on.
- `group`: a factor vector containing the group that the subject belongs to.
- `outcome`: a numeric vector containing the outcome variable. It might contain missing values. Additional baseline or time-varying covariates must be included in `data`.

`data` must have one row per visit per subject. This means that incomplete outcome data must be set as `NA` instead of having the related row missing. Missing values in the covariates are not allowed. If `data` is incomplete then the `expand_locf()` helper function can be used to insert any missing rows using Last Observation Carried Forward (LOCF) imputation to impute the covariates values. Note that LOCF is generally not a principled imputation method and should only be used when appropriate for the specific covariate.

Please note that there is no special provisioning for the baseline outcome values. If you do not want baseline observations to be included in the model as part of the response variable then these should be removed in advance from the outcome variable in `data`. At the same time if you want to include the baseline outcome as covariate in the model, then this should be included as a separate column of `data` (as any other covariate).

Character covariates will be explicitly cast to factors. If you use a custom analysis function that requires specific reference levels for the character covariates (for example in the computation of the least square means computation) then you are advised to manually cast your character covariates to factor in advance of running `draws()`.

The argument `data_ice` contains information about the occurrence of ICEs. It is a `data.frame` with 3 columns:

- **Subject ID**: a character vector containing the ids of the subjects that experienced the ICE. This column must be named as specified in `vars$subjid`.
- **Visit**: a character vector containing the first visit after the occurrence of the ICE (i.e. the first visit affected by the ICE). The visits must be equal to one of the levels of `data[[vars$visit]]`. If multiple ICEs happen for the same subject, then only the first non-MAR visit should be used. This column must be named as specified in `vars$visit`.
- **Strategy**: a character vector specifying the imputation strategy to address the ICE for this subject. This column must be named as specified in `vars$strategy`. Possible imputation strategies are:
  - `"MAR"`: Missing At Random.

- "CIR": Copy Increments in Reference.
- "CR": Copy Reference.
- "JR": Jump to Reference.
- "LMCF": Last Mean Carried Forward. For explanations of these imputation strategies, see Carpenter, Roger, and Kenward (2013), Cro et al (2021), and Wolbers et al (2022). Please note that user-defined imputation strategies can also be set.

The data_ice argument is necessary at this stage since (as explained in Wolbers et al (2022)), the model is fitted after removing the observations which are incompatible with the imputation model, i.e. any observed data on or after data_ice[[vars$visit]] that are addressed with an imputation strategy different from MAR are excluded for the model fit. However such observations will not be discarded from the data in the imputation phase (performed with the function (impute()). To summarize, **at this stage only pre-ICE data and post-ICE data that is after ICEs for which MAR imputation is specified are used**.

If the data_ice argument is omitted, or if a subject doesn't have a record within data_ice, then it is assumed that all of the relevant subject's data is pre-ICE and as such all missing visits will be imputed under the MAR assumption and all observed data will be used to fit the base imputation model. Please note that the ICE visit cannot be updated via the update_strategy argument in impute(); this means that subjects who didn't have a record in data_ice will always have their missing data imputed under the MAR assumption even if their strategy is updated.

The vars argument is a named list that specifies the names of key variables within data and data_ice. This list is created by set_vars() and contains the following named elements:

- subjid: name of the column in data and data_ice which contains the subject ids variable.
- visit: name of the column in data and data_ice which contains the visit variable.
- group: name of the column in data which contains the group variable.
- outcome: name of the column in data which contains the outcome variable.
- covariates: vector of characters which contains the covariates to be included in the model (including interactions which are specified as "covariateName1*covariateName2"). If no covariates are provided the default model specification of outcome ~ 1 + visit + group will be used. Please note that the group*visit interaction is **not** included in the model by default.
- strata: covariates used as stratification variables in the bootstrap sampling. By default only the vars$group is set as stratification variable. Needed only for method_condmean(type = "bootstrap") and method_approxbayes().
- strategy: name of the column in data_ice which contains the subject-specific imputation strategy.

In our experience, Bayesian MI (method = method_bayes()) with a relatively low number of samples (e.g. n_samples below 100) frequently triggers STAN warnings about R-hat such as "The largest R-hat is X.XX, indicating chains have not mixed". In many instances, this warning might be spurious, i.e. standard diagnostics analysis of the MCMC samples do not indicate any issues and results look reasonable. Increasing the number of samples to e.g. above 150 usually gets rid of the warning.

Value

A draws object which is a named list containing the following:

- `data`: R6 `longdata` object containing all relevant input data information.
- `method`: A `method` object as generated by either `method_bayes()`, `method_approxbayes()` or `method_condmean()`.
- `samples`: list containing the estimated parameters of interest. Each element of `samples` is a named list containing the following:
  - `ids`: vector of characters containing the ids of the subjects included in the original dataset.
  - `beta`: numeric vector of estimated regression coefficients.
  - `sigma`: list of estimated covariance matrices (one for each level of `vars$group`).
  - `theta`: numeric vector of transformed covariances.
  - `failed`: Logical. `TRUE` if the model fit failed.
  - `ids_samp`: vector of characters containing the ids of the subjects included in the given sample.
- `fit`: if `method_bayes()` is chosen, returns the MCMC Stan fit object. Otherwise `NULL`.
- `n_failures`: absolute number of failures of the model fit. Relevant only for `method_condmean(type = "bootstrap")`, `method_approxbayes()` and `method_bmlmi()`.
- `formula`: fixed effects formula object used for the model specification.

References

James R Carpenter, James H Roger, and Michael G Kenward. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. Journal of Biopharmaceutical Statistics, 23(6):1352–1371, 2013.

Suzie Cro, Tim P Morris, Michael G Kenward, and James R Carpenter. Sensitivity analysis for clinical trials with missing continuous outcome data using controlled multiple imputation: a practical guide. Statistics in Medicine, 39(21):2815–2842, 2020.

Roderick J. A. Little and Donald B. Rubin. Statistical Analysis with Missing Data, Second Edition. John Wiley & Sons, Hoboken, New Jersey, 2002. [Section 10.2.3]

Marcel Wolbers, Alessandro Noci, Paul Delmar, Craig Gower-Page, Sean Yiu, Jonathan W. Bartlett. Standard and reference-based conditional mean imputation. Pharmaceutical Statistics. 21(6): 1246-1257, 2022. doi:10.1002/pst.2234

Von Hippel, Paul T and Bartlett, Jonathan W. Maximum likelihood multiple imputation: Faster imputations and consistent standard errors without posterior draws. 2021.

See Also

`method_bayes()`, `method_approxbayes()`, `method_condmean()`, `method_bmlmi()` for setting `method`.

`set_vars()` for setting `vars`.

`expand_locf()` for expanding `data` in case of missing rows.

For more details see the quickstart vignette: `vignette("quickstart", package = "rbmi")`.

Examples

```
# Prepare the data: expand to one row per subject and visit
dat <- expand_locf(
    antidepressant_data,
    PATIENT = levels(antidepressant_data$PATIENT),
    VISIT = levels(antidepressant_data$VISIT),
    vars = c("BASVAL", "THERAPY"),
    group = c("PATIENT"),
    order = c("PATIENT", "VISIT")
)

# Derive data_ice: the first visit with a missing outcome for each patient is
# imputed under the Jump To Reference (JR) strategy. Subject 3618 has only an
# intermittent missing value and is removed (imputed under MAR by default).
is_missing <- is.na(dat$CHANGE)
dat_ice <- dat[is_missing, c("PATIENT", "VISIT")]
dat_ice <- dat_ice[!duplicated(dat_ice$PATIENT), ]
dat_ice$strategy <- "JR"
dat_ice <- dat_ice[dat_ice$PATIENT != 3618, ]

vars <- set_vars(
    outcome = "CHANGE",
    visit = "VISIT",
    subjid = "PATIENT",
    group = "THERAPY",
    covariates = c("BASVAL*VISIT", "THERAPY*VISIT")
)

# Conditional mean imputation with jackknife resampling (no rstan required)

drawObj <- draws(
    data = dat,
    data_ice = dat_ice,
    vars = vars,
    method = method_condmean(type = "jackknife"),
    quiet = TRUE
)
drawObj

# Bayesian imputation instead requires the rstan package
if (requireNamespace("rstan", quietly = TRUE)) {
    set.seed(987)
    drawObjBayes <- draws(
        data = dat,
        data_ice = dat_ice,
        vars = vars,
        method = method_bayes(
            n_samples = 150,
            control = control_bayes(warmup = 200, thin = 5, seed = 1821)
        ),
        quiet = TRUE
    )
```

```
    drawObjBayes
}
```

`eval_mmrm` *Evaluate a call to* `mmrm`

Description

This is a utility function that attempts to evaluate a call to `mmrm` managing any warnings or errors that are thrown.

Usage

```
eval_mmrm(expr)
```

Arguments

`expr`	An expression to be evaluated. Should be a call to `mmrm::mmrm()`.

Details

This function was originally developed for use with `glmmTMB` which needed more hand-holding and dropping of false-positive warnings. It is not as important now but is kept around encase we need to catch false-positive warnings again in the future.

See Also

`record()`

Examples

```
## Not run:
eval_mmrm({
    mmrm::mmrm(formula, data)
})

## End(Not run)
```

expand *Expand and fill in missing* data.frame *rows*

Description

These functions are essentially wrappers around base::expand.grid() to ensure that missing combinations of data are inserted into a data.frame with imputation/fill methods for updating covariate values of newly created rows.

Usage

```
expand(data, ...)

fill_locf(data, vars, group = NULL, order = NULL)

expand_locf(data, ..., vars, group, order)
```

Arguments

data	dataset to expand or fill in.
...	variables and the levels that should be expanded out (note that duplicate entries of levels will result in multiple rows for that level).
vars	character vector containing the names of variables that need to be filled in.
group	character vector containing the names of variables to group by when performing LOCF imputation of var.
order	character vector containing the names of additional variables to sort the data.frame by before performing LOCF.

Details

The draws() function makes the assumption that all subjects and visits are present in the data.frame and that all covariate values are non missing; expand(), fill_locf() and expand_locf() are utility functions to support users in ensuring that their data.frame's conform to these assumptions.

expand() takes vectors for expected levels in a data.frame and expands out all combinations inserting any missing rows into the data.frame. Note that all "expanded" variables are cast as factors.

fill_locf() applies LOCF imputation to named covariates to fill in any NAs created by the insertion of new rows by expand() (though do note that no distinction is made between existing NAs and newly created NAs). Note that the data.frame is sorted by c(group, order) before performing the LOCF imputation; the data.frame will be returned in the original sort order however.

expand_locf() a simple composition function of fill_locf() and expand() i.e. fill_locf(expand(...)).

Missing First Values:

The fill_locf() function performs last observation carried forward imputation. A natural consequence of this is that it is unable to impute missing observations if the observation is the first

value for a given subject / grouping. These values are deliberately not imputed as doing so risks silent errors in the case of time varying covariates. One solution is to first use `expand_locf()` on just the visit variable and time varying covariates and then merge on the baseline covariates afterwards i.e.

```
library(dplyr)

dat_expanded <- expand(
    data = dat,
    subject = c("pt1", "pt2", "pt3", "pt4"),
    visit = c("vis1", "vis2", "vis3")
)

dat_filled <- dat_expanded %>%
    left_join(baseline_covariates, by = "subject")
```

Value

A `data.frame` (of the same class as the input `data`). `expand()` returns `data` with all missing combinations of the expanded variables inserted as new rows, with the expanded variables cast to factors. `fill_locf()` returns `data` with the named `vars` imputed by last observation carried forward (in the original row order). `expand_locf()` returns the result of applying `fill_locf()` to the output of `expand()`.

Examples

```
## Not run:
dat_expanded <- expand(
    data = dat,
    subject = c("pt1", "pt2", "pt3", "pt4"),
    visit = c("vis1", "vis2", "vis3")
)

dat_filled <- fill_loc(
    data = dat_expanded,
    vars = c("Sex", "Age"),
    group = "subject",
    order = "visit"
)

## Or

dat_filled <- expand_locf(
    data = dat,
    subject = c("pt1", "pt2", "pt3", "pt4"),
    visit = c("vis1", "vis2", "vis3"),
    vars = c("Sex", "Age"),
    group = "subject",
    order = "visit"
)

## End(Not run)
```

`extract_covariates` *Extract Variables from string vector*

Description

Takes a string including potentially model terms like * and : and extracts out the individual variables

Usage

```
extract_covariates(x)
```

Arguments

x	string of variable names potentially including interaction terms

Details

i.e. `c("v1", "v2", "v2*v3", "v1:v2")` becomes `c("v1", "v2", "v3")`

`extract_data_mnar_as_na` *Set to NA outcome values that would be MNAR if they were missing (i.e. which occur after an ICE handled using a reference-based imputation strategy)*

Description

Set to NA outcome values that would be MNAR if they were missing (i.e. which occur after an ICE handled using a reference-based imputation strategy)

Usage

```
extract_data_mnar_as_na(longdata)
```

Arguments

longdata	R6 `longdata` object containing all relevant input data information.

Value

A `data.frame` containing `longdata$get_data(longdata$ids)`, but MNAR outcome values are set to `NA`.

extract_draws *Extract draws from a* stanfit *object*

Description

Extract draws from a stanfit object and convert them into lists.

The function rstan::extract() returns the draws for a given parameter as an array. This function calls rstan::extract() to extract the draws from a stanfit object and then convert the arrays into lists.

Usage

```
extract_draws(stan_fit, n_samples)
```

Arguments

stan_fit	A stanfit object.
n_samples	Number of MCMC draws.

Value

A named list of length 2 containing:

- beta: a list of length equal to n_samples containing the draws from the posterior distribution of the regression coefficients.
- sigma: a list of length equal to n_samples containing the draws from the posterior distribution of the covariance matrices. Each element of the list is a list with length equal to 1 if same_cov = TRUE or equal to the number of groups if same_cov = FALSE.

extract_imputed_df *Extract imputed dataset*

Description

Takes an imputation object as generated by imputation_df() and uses this to extract a completed dataset from a longdata object as created by longDataConstructor(). Also applies a delta transformation if a data.frame is provided to the delta argument. See analyse() for details on the structure of this data.frame.

Subject IDs in the returned data.frame are scrambled i.e. are not the original values.

Usage

```
extract_imputed_df(imputation, ld, delta = NULL, idmap = FALSE)
```

Arguments

imputation	An imputation object as generated by imputation_df().
ld	A longdata object as generated by longDataConstructor().
delta	Either NULL or a data.frame. Is used to offset outcome values in the imputed dataset.
idmap	Logical. If TRUE an attribute called idmap is attached to the return object which contains a list that maps the old subject ids the new subject ids.

Value

A data.frame.

---

extract_imputed_dfs *Extract imputed datasets*

Description

Extracts the imputed datasets contained within an imputations object generated by impute().

Usage

```
extract_imputed_dfs(
  imputations,
  index = seq_along(imputations$imputations),
  delta = NULL,
  idmap = FALSE
)
```

Arguments

imputations	An imputations object as created by impute().
index	The indexes of the imputed datasets to return. By default, all datasets within the imputations object will be returned.
delta	A data.frame containing the delta transformation to be applied to the imputed dataset. See analyse() for details on the format and specification of this data.frame.
idmap	Logical. The subject IDs in the imputed data.frame's are replaced with new IDs to ensure they are unique. Setting this argument to TRUE attaches an attribute, called idmap, to the returned data.frame's that will provide a map from the new subject IDs to the old subject IDs.

Value

A list of data.frames equal in length to the index argument.

See Also

`delta_template()` for creating delta data.frames.

`analyse()`.

Examples

```
## Not run:
extract_imputed_dfs(imputeObj)
extract_imputed_dfs(imputeObj, c(1:3))

## End(Not run)
```

`extract_params` *Extract parameters from a MMRM model*

Description

Extracts the beta and sigma coefficients from an MMRM model created by `mmrm::mmrm()`.

Usage

```
extract_params(fit)
```

Arguments

`fit`	an object created by `mmrm::mmrm()`

Details

For structured covariance models, additional parameter estimates will be returned, based on the type of the covariance model.

`fit_mcmc` *Fit the base imputation model using a Bayesian approach*

Description

`fit_mcmc()` fits the base imputation model using a Bayesian approach. This is done through a MCMC method that is implemented in Stan and is run by using the function `rstan::sampling()`. The function returns the draws from the posterior distribution of the model parameters and the `stanfit` object. Additionally it performs multiple diagnostics checks of the chain and returns warnings in case of any detected issues.

Usage

```
fit_mcmc(designmat, outcome, group, subjid, visit, method, quiet = FALSE)
```

Arguments

designmat	The design matrix of the fixed effects.
outcome	The response variable. Must be numeric.
group	Character vector containing the group variable.
subjid	Character vector containing the subjects IDs.
visit	Character vector containing the visit variable.
method	A method object as generated by method_bayes().
quiet	Specify whether the Stan sampling log should be printed to the console.

Details

The Bayesian model assumes a multivariate normal likelihood function and weakly-informative priors for the model parameters: in particular, uniform priors are assumed for the regression coefficients and inverse-Wishart priors for the covariance matrices. The chain is initialized using the REML parameter estimates from MMRM as starting values.

The function performs the following steps:

1. Fit MMRM using a REML approach.
2. Prepare the input data for the MCMC fit as described in the data{} block of the Stan file. See prepare_stan_data() for details.
3. Run the MCMC according the input arguments and using as starting values the REML parameter estimates estimated at point 1.
4. Performs diagnostics checks of the MCMC. See check_mcmc() for details.
5. Extract the draws from the model fit.

The chains perform method$n_samples draws by keeping one every method$burn_between iterations. Additionally the first method$burn_in iterations are discarded. The total number of iterations will then be method$burn_in + method$burn_between*method$n_samples. The purpose of method$burn_in is to ensure that the samples are drawn from the stationary distribution of the Markov Chain. The method$burn_between aims to keep the draws uncorrelated each from other.

Value

A named list composed by the following:

- samples: a named list containing the draws for each parameter. It corresponds to the output of extract_draws().
- fit: a stanfit object.

`fit_mmrm` *Fit a MMRM model*

Description

Fits a MMRM model allowing for different covariance structures using `mmrm::mmrm()`. Returns a `list` of key model parameters `beta`, `sigma` and an additional element `failed` indicating whether or not the fit failed to converge. If the fit did fail to converge `beta` and `sigma` will not be present.

Usage

```
fit_mmrm(
  designmat,
  outcome,
  subjid,
  visit,
  group,
  cov_struct = c("us", "ad", "adh", "ar1", "ar1h", "cs", "csh", "toep", "toeph"),
  REML = TRUE,
  same_cov = TRUE
)
```

Arguments

`designmat`	a `data.frame` or `matrix` containing the covariates to use in the MMRM model. Dummy variables must already be expanded out, i.e. via `stats::model.matrix()`. Cannot contain any missing values
`outcome`	a numeric vector. The outcome value to be regressed on in the MMRM model.
`subjid`	a character / factor vector. The subject identifier used to link separate visits that belong to the same subject.
`visit`	a character / factor vector. Indicates which visit the outcome value occurred on.
`group`	a character / factor vector. Indicates which treatment group the patient belongs to. Will internally be converted to a factor if it is a character vector.
`cov_struct`	a character value. Specifies which covariance structure to use. Must be one of `"us"` (default), `"ad"`, `"adh"`, `"ar1"`, `"ar1h"`, `"cs"`, `"csh"`, `"toep"`, or `"toeph"`)
`REML`	logical. Specifies whether restricted maximum likelihood should be used
`same_cov`	logical. Used to specify if a shared or individual covariance matrix should be used per `group`

format_method_descriptions *Format method descriptions*

Description

This function formats method descriptions by combining method names and their descriptions.

Usage

```
format_method_descriptions(method)
```

Arguments

method	A named list of methods and their descriptions.

Details

If any non-atomic elements are present in the method list, they are converted to a string representation using `dput()`.

Value

A character vector of formatted method descriptions.

generate_data_single *Generate data for a single group*

Description

Generate data for a single group

Usage

```
generate_data_single(pars_group, strategy_fun = NULL, distr_pars_ref = NULL)
```

Arguments

pars_group	A `simul_pars` object as generated by `set_simul_pars()`. It specifies the simulation parameters of the given group.
strategy_fun	Function implementing trajectories after the intercurrent event (ICE). Must be one of `getStrategies()`. See `getStrategies()` for details. If `NULL` then post-ICE outcomes are untouched.
distr_pars_ref	Optional. Named list containing the simulation parameters of the reference arm. It contains the following elements:

- `mu`: Numeric vector indicating the mean outcome trajectory assuming no ICEs. It should include the outcome at baseline.
- `sigma` Covariance matrix of the outcome trajectory assuming no ICEs. If `NULL`, then these parameters are inherited from `pars_group`.

Value

A `data.frame` containing the simulated data. It includes the following variables:

- `id`: Factor variable that specifies the id of each subject.
- `visit`: Factor variable that specifies the visit of each assessment. Visit `0` denotes the baseline visit.
- `group`: Factor variable that specifies which treatment group each subject belongs to.
- `outcome_bl`: Numeric variable that specifies the baseline outcome.
- `outcome_noICE`: Numeric variable that specifies the longitudinal outcome assuming no ICEs.
- `ind_ice1`: Binary variable that takes value `1` if the corresponding visit is affected by ICE1 and `0` otherwise.
- `dropout_ice1`: Binary variable that takes value `1` if the corresponding visit is affected by the drop-out following ICE1 and `0` otherwise.
- `ind_ice2`: Binary variable that takes value `1` if the corresponding visit is affected by ICE2.
- `outcome`: Numeric variable that specifies the longitudinal outcome including ICE1, ICE2 and the intermittent missing values.

See Also

`simulate_data()`.

`get_bootstrap_stack` *Creates a stack object populated with bootstrapped samples*

Description

Function creates a `Stack()` object and populated the stack with bootstrap samples based upon `method$n_samples`

Usage

```
get_bootstrap_stack(longdata, method, stack = Stack$new())
```

Arguments

`longdata`	A `longDataConstructor()` object
`method`	A `method` object
`stack`	A `Stack()` object (this is only exposed for unit testing purposes)

get_conditional_parameters *Derive conditional multivariate normal parameters*

Description

Takes parameters for a multivariate normal distribution and observed values to calculate the conditional distribution for the unobserved values.

Usage

```
get_conditional_parameters(pars, values)
```

Arguments

pars	a list with elements mu and sigma defining the mean vector and covariance matrix respectively.
values	a vector of observed values to condition on, must be same length as pars$mu. Missing values must be represented by an NA.

Value

A list with the conditional distribution parameters:

- mu - The conditional mean vector.
- sigma - The conditional covariance matrix.

get_delta_template *Get delta utility variables*

Description

This function creates the default delta template (1 row per subject per visit) and extracts all the utility information that users need to define their own logic for defining delta. See delta_template() for full details.

Usage

```
get_delta_template(imputations)
```

Arguments

imputations	an imputations object created by impute().

get_draws_mle *Fit the base imputation model on bootstrap samples*

Description

Fit the base imputation model using a ML/REML approach on a given number of bootstrap samples as specified by `method$n_samples`. Returns the parameter estimates from the model fit.

Usage

```
get_draws_mle(
  longdata,
  method,
  sample_stack,
  n_target_samples,
  first_sample_orig,
  use_samp_ids,
  failure_limit = 0,
  ncores = 1,
  quiet = FALSE
)
```

Arguments

`longdata`	R6 `longdata` object containing all relevant input data information.
`method`	A `method` object as generated by either `method_approxbayes()` or `method_condmean()` with argument `type = "bootstrap"`.
`sample_stack`	A stack object containing the subject ids to be used on each `mmrm` iteration.
`n_target_samples`	Number of samples needed to be created
`first_sample_orig`	Logical. If `TRUE` the function returns `method$n_samples + 1` samples where the first sample contains the parameter estimates from the original dataset and `method$n_samples` samples contain the parameter estimates from bootstrap samples. If `FALSE` the function returns `method$n_samples` samples containing the parameter estimates from bootstrap samples.
`use_samp_ids`	Logical. If `TRUE`, the sampled subject ids are returned. Otherwise the subject ids from the original dataset are returned. These values are used to tell `impute()` what subjects should be used to derive the imputed dataset.
`failure_limit`	Number of failed samples that are allowed before throwing an error
`ncores`	Number of processes to parallelise the job over
`quiet`	Logical, If `TRUE` will suppress printing of progress information that is printed to the console.

Details

This function takes a Stack object which contains multiple lists of patient ids. The function takes this Stack and pulls a set ids and then constructs a dataset just consisting of these patients (i.e. potentially a bootstrap or a jackknife sample).

The function then fits a MMRM model to this dataset to create a sample object. The function repeats this process until n_target_samples have been reached. If more than failure_limit samples fail to converge then the function throws an error.

After reaching the desired number of samples the function generates and returns a draws object.

Value

A draws object which is a named list containing the following:

- data: R6 longdata object containing all relevant input data information.
- method: A method object as generated by either method_bayes(), method_approxbayes() or method_condmean().
- samples: list containing the estimated parameters of interest. Each element of samples is a named list containing the following:
  - ids: vector of characters containing the ids of the subjects included in the original dataset.
  - beta: numeric vector of estimated regression coefficients.
  - sigma: list of estimated covariance matrices (one for each level of vars$group).
  - theta: numeric vector of transformed covariances.
  - failed: Logical. TRUE if the model fit failed.
  - ids_samp: vector of characters containing the ids of the subjects included in the given sample.
- fit: if method_bayes() is chosen, returns the MCMC Stan fit object. Otherwise NULL.
- n_failures: absolute number of failures of the model fit. Relevant only for method_condmean(type = "bootstrap"), method_approxbayes() and method_bmlmi().
- formula: fixed effects formula object used for the model specification.

---

get_ESS *Extract the Effective Sample Size (ESS) from a* stanfit *object*

Description

Extract the Effective Sample Size (ESS) from a stanfit object

Usage

```
get_ESS(stan_fit)
```

Arguments

stan_fit	A stanfit object.

Value

A named vector containing the ESS for each parameter of the model.

`get_ests_bmlmi` *Von Hippel and Bartlett pooling of BMLMI method*

Description

Compute pooled point estimates, standard error and degrees of freedom according to the Von Hippel and Bartlett formula for Bootstrapped Maximum Likelihood Multiple Imputation (BMLMI).

Usage

```
get_ests_bmlmi(ests, D)
```

Arguments

`ests`	numeric vector containing estimates from the analysis of the imputed datasets.
`D`	numeric representing the number of imputations between each bootstrap sample in the BMLMI method.

Details

`ests` must be provided in the following order: the firsts D elements are related to analyses from random imputation of one bootstrap sample. The second set of D elements (i.e. from D+1 to 2*D) are related to the second bootstrap sample and so on.

Value

a list containing point estimate, standard error and degrees of freedom.

References

Von Hippel, Paul T and Bartlett, Jonathan W8. Maximum likelihood multiple imputation: Faster imputations and consistent standard errors without posterior draws. 2021

`get_example_data` *Simulate a realistic example dataset*

Description

Simulate a realistic example dataset using `simulate_data()` with hard-coded values of all the input arguments.

Usage

```
get_example_data()
```

Details

`get_example_data()` simulates a 1:1 randomized trial of an active drug (intervention) versus placebo (control) with 100 subjects per group and 6 post-baseline assessments (bi-monthly visits until 12 months). One intercurrent event corresponding to treatment discontinuation is also simulated. Specifically, data are simulated under the following assumptions:

- The mean outcome trajectory in the placebo group increases linearly from 50 at baseline (visit 0) to 60 at visit 6, i.e. the slope is 10 points/year.
- The mean outcome trajectory in the intervention group is identical to the placebo group up to visit 2. From visit 2 onward, the slope decreases by 50% to 5 points/year.
- The covariance structure of the baseline and follow-up values in both groups is implied by a random intercept and slope model with a standard deviation of 5 for both the intercept and the slope, and a correlation of 0.25. In addition, an independent residual error with standard deviation 2.5 is added to each assessment.
- The probability of study drug discontinuation after each visit is calculated according to a logistic model which depends on the observed outcome at that visit. Specifically, a visit-wise discontinuation probability of 2% and 3% in the control and intervention group, respectively, is specified in case the observed outcome is equal to 50 (the mean value at baseline). The odds of a discontinuation is simulated to increase by +10% for each +1 point increase of the observed outcome.
- Study drug discontinuation is simulated to have no effect on the mean trajectory in the placebo group. In the intervention group, subjects who discontinue follow the slope of the mean trajectory from the placebo group from that time point onward. This is compatible with a copy increments in reference (CIR) assumption.
- Study drop-out at the study drug discontinuation visit occurs with a probability of 50% leading to missing outcome data from that time point onward.

Value

A `data.frame` of simulated longitudinal trial data (as produced by `simulate_data()`) with 100 subjects per group across 7 visits, suitable for demonstrating the `rbmi` workflow. It contains the subject id, group, visit, outcome and covariate columns together with the intercurrent-event and missingness indicators generated by the simulation.

See Also

simulate_data(), set_simul_pars()

Examples

```
set.seed(1974)
dat <- get_example_data()
head(dat)
```

---

get_jackknife_stack *Creates a stack object populated with jackknife samples*

Description

Function creates a Stack() object and populated the stack with jackknife samples based upon

Usage

```
get_jackknife_stack(longdata, method, stack = Stack$new())
```

Arguments

longdata	A longDataConstructor() object
method	A method object
stack	A Stack() object (this is only exposed for unit testing purposes)

---

get_mmrm_sample *Fit MMRM and returns parameter estimates*

Description

get_mmrm_sample fits the base imputation model using a ML/REML approach. Returns the parameter estimates from the fit.

Usage

```
get_mmrm_sample(ids, longdata, method)
```

Arguments

ids	vector of characters containing the ids of the subjects.
longdata	R6 longdata object containing all relevant input data information.
method	A method object as generated by either method_approxbayes() or method_condmean().

Value

A named list of class `sample_single`. It contains the following:

- `ids` vector of characters containing the ids of the subjects included in the original dataset.
- `beta` numeric vector of estimated regression coefficients.
- `sigma` list of estimated covariance matrices (one for each level of `vars$group`).
- `theta` numeric vector of transformed covariances.
- `failed` logical. `TRUE` if the model fit failed.
- `ids_samp` vector of characters containing the ids of the subjects included in the given sample.

`get_pattern_groups` *Determine patients missingness group*

Description

Takes a design matrix with multiple rows per subject and returns a dataset with 1 row per subject with a new column `pgroup` indicating which group the patient belongs to (based upon their missingness pattern and treatment group)

Usage

```
get_pattern_groups(ddat)
```

Arguments

`ddat`	a `data.frame` with columns `subjid`, `visit`, `group`, `is_avail`

Details

- The column `is_avail` must be a character or numeric `0` or `1`

`get_pattern_groups_unique` *Get Pattern Summary*

Description

Takes a dataset of pattern information and creates a summary dataset of it with just 1 row per pattern

Usage

```
get_pattern_groups_unique(patterns)
```

Arguments

patterns	A data.frame with the columns pgroup, pattern and group

Details

- The column pgroup must be a numeric vector indicating which pattern group the patient belongs to
- The column pattern must be a character string of 0's or 1's. It must be identical for all rows within the same pgroup
- The column group must be a character / numeric vector indicating which covariance group the observation belongs to. It must be identical within the same pgroup

---

get_pool_components *Expected Pool Components*

Description

Returns the elements expected to be contained in the analyse object depending on what analysis method was specified.

Usage

```
get_pool_components(x)
```

Arguments

x	Character name of the analysis method, must one of either "rubin", "jackknife", "bootstrap" or "bmlmi".

---

get_visit_distribution_parameters *Derive visit distribution parameters*

Description

Takes patient level data and beta coefficients and expands them to get a patient specific estimate for the visit distribution parameters mu and sigma. Returns the values in a specific format which is expected by downstream functions in the imputation process (namely list(list(mu = ..., sigma = ...), list(mu = ..., sigma = ...))).

Usage

```
get_visit_distribution_parameters(dat, beta, sigma)
```

Arguments

dat	Patient level dataset, must be 1 row per visit. Column order must be in the same order as beta. The number of columns must match the length of beta
beta	List of model beta coefficients. There should be 1 element for each sample e.g. if there were 3 samples and the models each had 4 beta coefficients then this argument should be of the form `list( c(1,2,3,4) , c(5,6,7,8), c(9,10,11,12))`. All elements of beta must be the same length and must be the same length and order as `dat`.
sigma	List of sigma. Must have the same number of entries as `beta`.

---

getStrategies *Get imputation strategies*

Description

Returns a list defining the imputation strategies to be used to create the multivariate normal distribution parameters by merging those of the source group and reference group per patient.

Usage

```
getStrategies(...)
```

Arguments

...	User defined methods to be added to the return list. Input must be a function.

Details

By default Jump to Reference (JR), Copy Reference (CR), Copy Increments in Reference (CIR), Last Mean Carried Forward (LMCF) and Missing at Random (MAR) are defined.

The user can define their own strategy functions (or overwrite the pre-defined ones) by specifying a named input to the function i.e. `NEW = function(...) ...`. Only exception is MAR which cannot be overwritten.

All user defined functions must take 3 inputs: `pars_group`, `pars_ref` and `index_mar`. `pars_group` and `pars_ref` are both lists with elements `mu` and `sigma` representing the multivariate normal distribution parameters for the subject's current group and reference group respectively. `index_mar` will be a logical vector specifying which visits the subject met the MAR assumption at. The function must return a list with elements `mu` and `sigma`. See the implementation of `strategy_JR()` for an example.

Value

A named list of imputation strategy functions. By default this contains the built-in strategies `JR`, `CR`, `CIR`, `LMCF` and `MAR`, together with (or overwritten by) any user-defined strategies supplied via `...`. Each element is a function taking `pars_group`, `pars_ref` and `index_mar`.

Examples

```
## Not run:
getStrategies()
getStrategies(
    NEW = function(pars_group, pars_ref, index_mar) code ,
    JR = function(pars_group, pars_ref, index_mar)  more_code
)

## End(Not run)
```

`ife` *if else*

Description

A wrapper around `if() else()` to prevent unexpected interactions between `ifelse()` and factor variables

Usage

```
ife(x, a, b)
```

Arguments

`x`	True / False
`a`	value to return if True
`b`	value to return if False

Details

By default `ifelse()` will convert factor variables to their numeric values which is often undesirable. This connivance function avoids that problem

---

`imputation_df` *Create a valid* `imputation_df` *object*

Description

Create a valid `imputation_df` object

Usage

```
imputation_df(...)
```

Arguments

`...`	a list of `imputation_single`.

imputation_list_df *List of* imputation_df*s*

Description

A container for multiple imputation_df's

Usage

```
imputation_list_df(...)
```

Arguments

...	objects of class imputation_df

imputation_list_single *A collection of* imputation_singles() *grouped by a single* subjid *ID*

Description

A collection of imputation_singles() grouped by a single subjid ID

Usage

```
imputation_list_single(imputations, D = 1)
```

Arguments

imputations	a list of imputation_single() objects ordered so that repetitions are grouped sequentially
D	the number of repetitions that were performed which determines how many columns the imputation matrix should have

This is a constructor function to create a imputation_list_single object which contains a matrix of imputation_single() objects grouped by a single id. The matrix is split so that it has D columns (i.e. for non-BMLMI methods this will always be 1)

The id attribute is determined by extracting the id attribute from the contributing imputation_single() objects. An error is throw if multiple id are detected

imputation_single *Create a valid* imputation_single *object*

Description

Create a valid imputation_single object

Usage

```
imputation_single(id, values)
```

Arguments

id	a character string specifying the subject id.
values	a numeric vector indicating the imputed values.

impute *Create imputed datasets*

Description

impute() creates imputed datasets based upon the data and options specified in the call to draws(). One imputed dataset is created per each "sample" created by draws().

Usage

```
impute(
  draws,
  references = NULL,
  update_strategy = NULL,
  strategies = getStrategies()
)

## S3 method for class 'random'
impute(
  draws,
  references = NULL,
  update_strategy = NULL,
  strategies = getStrategies()
)

## S3 method for class 'condmean'
impute(
  draws,
  references = NULL,
```

```
  update_strategy = NULL,
  strategies = getStrategies()
)
```

Arguments

draws	A draws object created by draws().
references	A named vector. Identifies the references to be used for reference-based imputation methods. Should be of the form c("Group1" = "Reference1", "Group2" = "Reference2"). If NULL (default), the references are assumed to be of the form c("Group1" = "Group1", "Group2" = "Group2"). This argument cannot be NULL if an imputation strategy (as defined by data_ice[[vars$strategy]] in the call to draws) other than MAR is set.
update_strategy	An optional data.frame. Updates the imputation method that was originally set via the data_ice option in draws(). See the details section for more information.
strategies	A named list of functions. Defines the imputation functions to be used. The names of the list should mirror the values specified in strategy column of data_ice. Default = getStrategies(). See getStrategies() for more details.

Details

impute() uses the imputation model parameter estimates, as generated by draws(), to first calculate the marginal (multivariate normal) distribution of a subject's longitudinal outcome variable depending on their covariate values. For subjects with intercurrent events (ICEs) handled using non-MAR methods, this marginal distribution is then updated depending on the time of the first visit affected by the ICE, the chosen imputation strategy and the chosen reference group as described in Carpenter, Roger, and Kenward (2013) . The subject's imputation distribution used for imputing missing values is then defined as their marginal distribution conditional on their observed outcome values. One dataset is being generated per set of parameter estimates provided by draws().

The exact manner in how missing values are imputed from this conditional imputation distribution depends on the method object that was provided to draws(), in particular:

- Bayes & Approximate Bayes: each imputed dataset contains 1 row per subject & visit from the original dataset with missing values imputed by taking a single random sample from the conditional imputation distribution.
- Conditional Mean: each imputed dataset contains 1 row per subject & visit from the bootstrapped or jackknife dataset that was used to generate the corresponding parameter estimates in draws(). Missing values are imputed by using the mean of the conditional imputation distribution. Please note that the first imputed dataset refers to the conditional mean imputation on the original dataset whereas all subsequent imputed datasets refer to conditional mean imputations for bootstrap or jackknife samples, respectively, of the original data.
- Bootstrapped Maximum Likelihood MI (BMLMI): it performs D random imputations of each bootstrapped dataset that was used to generate the corresponding parameter estimates in draws(). A total number of B*D imputed datasets is provided, where B is the number of bootstrapped

datasets. Missing values are imputed by taking a random sample from the conditional imputation distribution.

The update_strategy argument can be used to update the imputation strategy that was originally set via the data_ice option in draws(). This avoids having to re-run the draws() function when changing the imputation strategy in certain circumstances (as detailed below). The data.frame provided to update_strategy argument must contain two columns, one for the subject ID and another for the imputation strategy, whose names are the same as those defined in the vars argument as specified in the call to draws(). Please note that this argument only allows you to update the imputation strategy and not other arguments such as the time of the first visit affected by the ICE. A key limitation of this functionality is that one can only switch between a MAR and a non-MAR strategy (or vice versa) for subjects without observed post-ICE data. The reason for this is that such a change would affect whether the post-ICE data is included in the base imputation model or not (as explained in the help to draws()). As an example, if a subject had their ICE on "Visit 2" but had observed/known values for "Visit 3" then the function will throw an error if one tries to switch the strategy from MAR to a non-MAR strategy. In contrast, switching from a non-MAR to a MAR strategy, whilst valid, will raise a warning as not all usable data will have been utilised in the imputation model.

Value

An imputation object; a list of class "imputation" containing the original longitudinal data, a list of imputations (one entry per imputed dataset, each recording the imputed values needed to reconstruct a completed dataset) and the method used. This object is typically passed on to analyse(); the completed datasets can be extracted with extract_imputed_dfs().

References

James R Carpenter, James H Roger, and Michael G Kenward. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. Journal of Biopharmaceutical Statistics, 23(6):1352–1371, 2013. [Section 4.2 and 4.3]

Examples

```
## Not run:

impute(
    draws = drawobj,
    references = c("Trt" = "Placebo", "Placebo" = "Placebo")
)

new_strategy <- data.frame(
  subjid = c("Pt1", "Pt2"),
  strategy = c("MAR", "JR")
)

impute(
    draws = drawobj,
    references = c("Trt" = "Placebo", "Placebo" = "Placebo"),
    update_strategy = new_strategy
)
```

```
## End(Not run)
```

`impute_data_individual` *Impute data for a single subject*

Description

This function performs the imputation for a single subject at a time implementing the process as detailed in `impute()`.

Usage

```
impute_data_individual(
  id,
  index,
  beta,
  sigma,
  data,
  references,
  strategies,
  condmean,
  n_imputations = 1
)
```

Arguments

`id`	Character string identifying the subject.
`index`	The sample indexes which the subject belongs to e.g `c(1,1,1,2,2,4)`.
`beta`	A list of beta coefficients for each sample, i.e. `beta[[1]]` is the set of beta coefficients for the first sample.
`sigma`	A list of the sigma coefficients for each sample split by group i.e. `sigma[[1]][["A"]]` would give the sigma coefficients for group A for the first sample.
`data`	A `longdata` object created by `longDataConstructor()`
`references`	A named vector. Identifies the references to be used when generating the imputed values. Should be of the form `c("Group" = "Reference", "Group" = "Reference")`.
`strategies`	A named list of functions. Defines the imputation functions to be used. The names of the list should mirror the values specified in `method` column of `data_ice`. Default = `getStrategies()`. See `getStrategies()` for more details.
`condmean`	Logical. If `TRUE` will impute using the conditional mean values, if `FALSE` will impute by taking a random draw from the multivariate normal distribution.
`n_imputations`	When `condmean = FALSE` numeric representing the number of random imputations to be performed for each sample. Default is `1` (one random imputation per sample).

Details

Note that this function performs all of the required imputations for a subject at the same time. I.e. if a subject is included in samples 1,3,5,9 then all imputations (using sample-dependent imputation model parameters) are performed in one step in order to avoid having to look up a subjects' covariates and expanding them to a design matrix multiple times (which would be more computationally expensive). The function also supports subject belonging to the same sample multiple times, i.e. 1,1,2,3,5,5, as will typically occur for bootstrapped datasets.

`impute_internal` *Create imputed datasets*

Description

This is the work horse function that implements most of the functionality of impute. See the user level function `impute()` for further details.

Usage

```
impute_internal(
  draws,
  references = NULL,
  update_strategy,
  strategies,
  condmean
)
```

Arguments

`draws`	A `draws` object created by `draws()`.
`references`	A named vector. Identifies the references to be used for reference-based imputation methods. Should be of the form `c("Group1" = "Reference1", "Group2" = "Reference2")`. If `NULL` (default), the references are assumed to be of the form `c("Group1" = "Group1", "Group2" = "Group2")`. This argument cannot be `NULL` if an imputation strategy (as defined by `data_ice[[vars$strategy]]` in the call to draws) other than `MAR` is set.
`update_strategy`	An optional `data.frame`. Updates the imputation method that was originally set via the `data_ice` option in `draws()`. See the details section for more information.
`strategies`	A named list of functions. Defines the imputation functions to be used. The names of the list should mirror the values specified in `strategy` column of `data_ice`. Default = `getStrategies()`. See `getStrategies()` for more details.
`condmean`	logical. If TRUE will impute using the conditional mean values, if values will impute by taking a random draw from the multivariate normal distribution.

impute_outcome *Sample outcome value*

Description

Draws a random sample from a multivariate normal distribution.

Usage

```
impute_outcome(conditional_parameters, n_imputations = 1, condmean = FALSE)
```

Arguments

conditional_parameters	a list with elements mu and sigma which contain the mean vector and covariance matrix to sample from.
n_imputations	numeric representing the number of random samples from the multivariate normal distribution to be performed. Default is 1.
condmean	should conditional mean imputation be performed (as opposed to random sampling)

invert *invert*

Description

Utility function used to replicate purrr::transpose. Turns a list inside out.

Usage

```
invert(x)
```

Arguments

x	list

invert_indexes *Invert and derive indexes*

Description

Takes a list of elements and creates a new list containing 1 entry per unique element value containing the indexes of which original elements it occurred in.

Usage

```
invert_indexes(x)
```

Arguments

x	list of elements to invert and calculate index from (see details).

Details

This functions purpose is best illustrated by an example:

input:

```
list( c("A", "B", "C"), c("A", "A", "B"))}
```

becomes:

```
list( "A" = c(1,2,2), "B" = c(1,2), "C" = 1 )
```

is_absent *Is value absent*

Description

Returns true if a value is either NULL, NA or "". In the case of a vector all values must be NULL/NA/"" for x to be regarded as absent.

Usage

```
is_absent(x, na = TRUE, blank = TRUE)
```

Arguments

x	a value to check if it is absent or not
na	do NAs count as absent
blank	do blanks i.e. "" count as absent

is_char_fact *Is character or factor*

Description

returns true if x is character or factor vector

Usage

```
is_char_fact(x)
```

Arguments

x	a character or factor vector

is_char_one *Is single character*

Description

returns true if x is a length 1 character vector

Usage

```
is_char_one(x)
```

Arguments

x	a character vector

is_in_rbmi_development *Is package in development mode?*

Description

Returns TRUE if the package is being developed on i.e. you have a local copy of the source code which you are actively editing Returns FALSE otherwise

Usage

```
is_in_rbmi_development()
```

Details

Main use of this function is in parallel processing to indicate whether the sub-processes need to load the current development version of the code or whether they should load the main installed package on the system

---

is_num_char_fact *Is character, factor or numeric*

Description

returns true if x is a character, numeric or factor vector

Usage

```
is_num_char_fact(x)
```

Arguments

x	a character, numeric or factor vector

---

locf *Last Observation Carried Forward*

Description

Returns a vector after applied last observation carried forward imputation.

Usage

```
locf(x)
```

Arguments

x	a vector.

Value

A vector of the same length as x in which each NA has been replaced by the most recent preceding non-NA value. Leading NAs (those with no earlier value to carry forward) are left unchanged.

Examples

```
## Not run:
locf(c(NA, 1, 2, 3, NA, 4)) # Returns c(NA, 1, 2, 3, 3, 4)

## End(Not run)
```

ls_design *Calculate design vector for the lsmeans*

Description

Calculates the design vector as required to generate the lsmean and standard error. `ls_design_equal` calculates it by applying an equal weight per covariate combination whilst `ls_design_proportional` applies weighting proportional to the frequency in which the covariate combination occurred in the actual dataset.

Usage

```
ls_design_equal(data, frm, fix)

ls_design_counterfactual(data, frm, fix)

ls_design_proportional(data, frm, fix)
```

Arguments

`data`	A data.frame
`frm`	Formula used to fit the original model
`fix`	A named list of variables with fixed values

lsmeans *Least Square Means*

Description

Estimates the least square means from a linear model. The exact implementation / interpretation depends on the weighting scheme; see the weighting section for more information.

Usage

```
lsmeans(
  model,
  ...,
  .weights = c("counterfactual", "equal", "proportional_em", "proportional")
)
```

Arguments

model	A model created by lm.
...	Fixes specific variables to specific values i.e. trt = 1 or age = 50. The name of the argument must be the name of the variable within the dataset.
.weights	Character, either "counterfactual" (default), "equal", "proportional_em" or "proportional". Specifies the weighting strategy to be used when calculating the lsmeans. See the weighting section for more details.

Weighting

Counterfactual:

For weights = "counterfactual" (the default) the lsmeans are obtained by taking the average of the predicted values for each patient after assigning all patients to each arm in turn. This approach is equivalent to standardization or g-computation. In comparison to emmeans this approach is equivalent to:

```
emmeans::emmeans(model, specs = "<treatment>", counterfactual = "<treatment>")
```

Note that to ensure backwards compatibility with previous versions of rbmi weights = "proportional" is an alias for weights = "counterfactual". To get results consistent with emmeans's weights = "proportional" please use weights = "proportional_em".

Equal:

For weights = "equal" the lsmeans are obtained by taking the model fitted value of a hypothetical patient whose covariates are defined as follows:

- Continuous covariates are set to mean(X)
- Dummy categorical variables are set to 1/N where N is the number of levels
- Continuous * continuous interactions are set to mean(X) * mean(Y)
- Continuous * categorical interactions are set to mean(X) * 1/N
- Dummy categorical * categorical interactions are set to 1/N * 1/M

In comparison to emmeans this approach is equivalent to:

```
emmeans::emmeans(model, specs = "<treatment>", weights = "equal")
```

Proportional:

For weights = "proportional_em" the lsmeans are obtained as per weights = "equal" except instead of weighting each observation equally they are weighted by the proportion in which the given combination of categorical values occurred in the data. In comparison to emmeans this approach is equivalent to:

```
emmeans::emmeans(model, specs = "<treatment>", weights = "proportional")
```

Note that this is not to be confused with weights = "proportional" which is an alias for weights = "counterfactual".

Fixing

Regardless of the weighting scheme any named arguments passed via ... will fix the value of the covariate to the specified value. For example, `lsmeans(model, trt = "A")` will fix the dummy variable `trtA` to 1 for all patients (real or hypothetical) when calculating the lsmeans.

See the references for similar implementations as done in SAS and in R via the `emmeans` package.

References

https://CRAN.R-project.org/package=emmeans

https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.3/statug/statug_glm_details41.htm

Examples

```
## Not run:
mod <- lm(Sepal.Length ~ Species + Petal.Length, data = iris)
lsmeans(mod)
lsmeans(mod, Species = "virginica")
lsmeans(mod, Species = "versicolor")
lsmeans(mod, Species = "versicolor", Petal.Length = 1)

## End(Not run)
```

`make_rbmi_cluster` *Create a* `rbmi` *ready cluster*

Description

Create a `rbmi` ready cluster

Usage

```
make_rbmi_cluster(ncores = 1, objects = NULL, packages = NULL)
```

Arguments

`ncores`	Number of parallel processes to use or an existing cluster to make use of
`objects`	a named list of objects to export into the sub-processes
`packages`	a character vector of libraries to load in the sub-processes

This function is a wrapper around `parallel::makePSOCKcluster()` but takes care of configuring `rbmi` to be used in the sub-processes as well as loading user defined objects and libraries and setting the seed for reproducibility.

If `ncores` is `1` this function will return `NULL`.

If `ncores` is a cluster created via `parallel::makeCluster()` then this function just takes care of inserting the relevant `rbmi` objects into the existing cluster.

Value

A parallel socket cluster object (as created by `parallel::makePSOCKcluster()`) configured for use with `rbmi`, or `NULL` if `ncores = 1`. When `ncores` is an existing cluster it is returned with the required `rbmi` objects and libraries loaded into it.

Examples

```
## Not run:
# Basic usage
make_rbmi_cluster(5)

# User objects + libraries
VALUE <- 5
myfun <- function(x) {
    x + day(VALUE) # From lubridate::day()
}
make_rbmi_cluster(5, list(VALUE = VALUE, myfun = myfun), c("lubridate"))

# Using a already created cluster
cl <- parallel::makeCluster(5)
make_rbmi_cluster(cl)

## End(Not run)
```

---

method *Set the multiple imputation methodology*

Description

These functions determine what methods `rbmi` should use when creating the imputation models, generating imputed values and pooling the results.

Usage

```
method_bayes(
  covariance = c("us", "ad", "adh", "ar1", "ar1h", "cs", "csh", "toep", "toeph"),
  same_cov = TRUE,
  n_samples = 20,
  prior_cov = c("default", "lkj"),
  control = control_bayes(),
  burn_in = NULL,
  burn_between = NULL
)

method_approxbayes(
  covariance = c("us", "ad", "adh", "ar1", "ar1h", "cs", "csh", "toep", "toeph"),
  threshold = 0.01,
  same_cov = TRUE,
```

```
  REML = TRUE,
  n_samples = 20
)

method_condmean(
  covariance = c("us", "ad", "adh", "ar1", "ar1h", "cs", "csh", "toep", "toeph"),
  threshold = 0.01,
  same_cov = TRUE,
  REML = TRUE,
  n_samples = NULL,
  type = c("bootstrap", "jackknife")
)

method_bmlmi(
  covariance = c("us", "ad", "adh", "ar1", "ar1h", "cs", "csh", "toep", "toeph"),
  threshold = 0.01,
  same_cov = TRUE,
  REML = TRUE,
  B = 20,
  D = 2
)
```

Arguments

covariance	a character string that specifies the structure of the covariance matrix to be used in the imputation model. Must be one of "us" (default), "ad", "adh", "ar1", "ar1h", "cs", "csh", "toep", or "toeph"). See details.
same_cov	a logical, if TRUE the imputation model will be fitted using a single shared covariance matrix for all observations. If FALSE a separate covariance matrix will be fit for each group as determined by the group argument of set_vars().
n_samples	a numeric that determines how many imputed datasets are generated. In the case of method_condmean(type = "jackknife") this argument must be set to NULL. See details.
prior_cov	a character string that specifies the prior used for the covariance model parameters. Must be one of "default" (default) or "lkj" (for the unstructured covariance model). See the Statistical Specifications vignette for details.
control	a list which specifies further lower level details of the computations. Currently only used by method_bayes(), please see control_bayes() for details and default settings.
burn_in	deprecated. Please use the warmup argument in control_bayes() instead.
burn_between	deprecated. Please use the thin argument in control_bayes() instead.
threshold	a numeric between 0 and 1, specifies the proportion of bootstrap datasets that can fail to produce valid samples before an error is thrown. See details.
REML	a logical indicating whether to use REML estimation rather than maximum likelihood.

type	a character string that specifies the resampling method used to perform inference when a conditional mean imputation approach (set via method_condmean()) is used. Must be one of "bootstrap" or "jackknife".
B	a numeric that determines the number of bootstrap samples for method_bmlmi.
D	a numeric that determines the number of random imputations for each bootstrap sample. Needed for method_bmlmi().

Details

In the case of method_condmean(type = "bootstrap") there will be n_samples + 1 imputation models and datasets generated as the first sample will be based on the original dataset whilst the other n_samples samples will be bootstrapped datasets. Likewise, for method_condmean(type = "jackknife") there will be length(unique(data$subjid)) + 1 imputation models and datasets generated. In both cases this is represented by n + 1 being displayed in the print message. In the case that method_bayes() is used, and with the control argument the number of chains is set to more than 1, then the n_samples samples will be distributed across the chains. The total number of returned samples will still be n_samples.

The user is able to specify different covariance structures using the the covariance argument. Currently supported structures include:

- Unstructured ("us") (default)
- Ante-dependence ("ad")
- Heterogeneous ante-dependence ("adh")
- First-order auto-regressive ("ar1")
- Heterogeneous first-order auto-regressive ("ar1h")
- Compound symmetry ("cs")
- Heterogeneous compound symmetry ("csh")
- Toeplitz ("toep")
- Heterogeneous Toeplitz ("toeph")

For full details please see mmrm::cov_types().

In the case of method_condmean(type = "bootstrap"), method_approxbayes() and method_bmlmi() repeated bootstrap samples of the original dataset are taken with an MMRM fitted to each sample. Due to the randomness of these sampled datasets, as well as limitations in the optimisers used to fit the models, it is not uncommon that estimates for a particular dataset can't be generated. In these instances rbmi is designed to throw out that bootstrapped dataset and try again with another. However to ensure that these errors are due to chance and not due to some underlying misspecification in the data and/or model a tolerance limit is set on how many samples can be discarded. Once the tolerance limit has been reached an error will be thrown and the process aborted. The tolerance limit is defined as ceiling(threshold * n_samples). Note that for the jackknife method estimates need to be generated for all leave-one-out datasets and as such an error will be thrown if any of them fail to fit.

Please note that at the time of writing (September 2021) Stan is unable to produce reproducible samples across different operating systems even when the same seed is used. As such care must be taken when using Stan across different machines. For more information on this limitation please consult the Stan documentation https://mc-stan.org/docs/2_27/reference-manual/reproducibility-chapter.html

Value

A method object; a named list of class c("method", <type>) where <type> is one of "bayes", "approxbayes", "condmean" or "bmlmi". It stores the chosen imputation methodology and its settings and is passed to the method argument of draws().

Examples

```
# Bayesian multiple imputation with 150 imputed datasets
method_bayes(
    n_samples = 150,
    control = control_bayes(warmup = 200, thin = 5)
)

# Approximate Bayesian multiple imputation with 20 imputed datasets
method_approxbayes(n_samples = 20)

# Conditional mean imputation with jackknife resampling
method_condmean(type = "jackknife")

# Conditional mean imputation with 100 bootstrap samples
method_condmean(type = "bootstrap", n_samples = 100)

# Bootstrapped maximum likelihood multiple imputation with D = 2 random
# imputations for each bootstrap sample and B = 20 bootstrap samples
method_bmlmi(B = 20, D = 2)
```

---

par_lapply *Parallelise* lapply

Description

Simple wrapper around lapply and parallel::clusterApplyLB to abstract away the logic of deciding which one to use

Usage

```
par_lapply(cl, fun, x, ...)
```

Arguments

cl	Cluster created by parallel::makeCluster() or NULL
fun	Function to be run
x	object to be looped over
...	extra arguments passed to fun

parametric_ci *Calculate parametric confidence intervals*

Description

Calculates confidence intervals based upon a parametric distribution.

Usage

```
parametric_ci(point, se, alpha, alternative, qfun, pfun, ...)
```

Arguments

point	The point estimate.
se	The standard error of the point estimate. If using a non-"normal" distribution this should be set to 1.
alpha	The type 1 error rate, should be a value between 0 and 1.
alternative	a character string specifying the alternative hypothesis, must be one of "two.sided" (default), "greater" or "less".
qfun	The quantile function for the assumed distribution i.e. qnorm.
pfun	The CDF function for the assumed distribution i.e. pnorm.
...	additional arguments passed on qfun and pfun i.e. df = 102.

pool *Pool analysis results obtained from the imputed datasets*

Description

Pool analysis results obtained from the imputed datasets

Usage

```
pool(
  results,
  conf.level = 0.95,
  alternative = c("two.sided", "less", "greater"),
  type = c("percentile", "normal"),
  rubin_df_method = c("barnard-rubin", "rubin")
)

## S3 method for class 'pool'
as.data.frame(x, ...)
```

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

mcse(x, results)

## S3 method for class 'mcse'
as.data.frame(x, ...)

## S3 method for class 'mcse'
print(x, ..., pval_digits = 2, pval_eps = 1e-06, pval_nsmall = 5)
```

Arguments

results	an analysis object created by analyse().
conf.level	confidence level of the returned confidence interval. Must be a single number between 0 and 1. Default is 0.95.
alternative	a character string specifying the alternative hypothesis, must be one of "two.sided" (default), "greater" or "less".
type	a character string of either "percentile" (default) or "normal". Determines what method should be used to calculate the bootstrap confidence intervals. See details. Only used if method_condmean(type = "bootstrap") was specified in the original call to draws().
rubin_df_method	a character string specifying the degrees-of-freedom approximation used when pooling with Rubin's rules. "barnard-rubin" (default) uses the Barnard-Rubin (1999) small-sample adjustment, while "rubin" uses the approximation from Rubin (1987). Ignored for other pooling methods.
x	a pool object generated by pool().
...	not used.
pval_digits	number of significant digits to print for p-values' MCSE.
pval_eps	the minimum p-values' MCSE to print.
pval_nsmall	the minimum number of digits to print for p-values' MCSE.

Details

The calculation used to generate the point estimate, standard errors and confidence interval depends upon the method specified in the original call to draws(); In particular:

- method_approxbayes() & method_bayes() both use Rubin's rules to pool estimates and variances across multiple imputed datasets. By default, the Barnard-Rubin (1999) rule is used to pool degrees of freedom; set rubin_df_method = "rubin" to use the original approximation from Rubin (1987). Here, the mcse() function can compute the Monte Carlo standard error (MCSE) of the pooled estimates, via a Jackknife variance estimator for all parameters; see Efron & Gong (1983) and Royston, Carlin & White (2009).
- method_condmean(type = "bootstrap") uses percentile or normal approximation; see Efron & Tibshirani (1994). Note that for the percentile bootstrap, no standard error is calculated, i.e. the standard errors will be NA in the object / data.frame.

- `method_condmean(type = "jackknife")` uses the standard jackknife variance formula; see Efron & Tibshirani (1994).
- `method_bmlmi` uses pooling procedure for Bootstrapped Maximum Likelihood MI (BMLMI). See Von Hippel & Bartlett (2021).

Value

A `pool` object; a list of class `"pool"` containing the pooled analysis results with the following elements:

- `pars`: a named list with one entry per parameter, each itself a list containing the pooled point estimate (`est`), confidence interval (`ci`), standard error (`se`) and p-value (`pvalue`).
- `conf.level`: the confidence level used for the confidence intervals.
- `alternative`: the alternative hypothesis used to derive the p-values.
- `N`: the number of analysis results that were combined.
- `method`: the pooling method that was used.

The `as.data.frame()` method returns a `data.frame` with one row per parameter (columns `parameter`, `est`, `se`, `lci`, `uci`, `pval`) and the `print()` method returns its input invisibly. When the analysis function attached per-parameter metadata (as `ancova()` does), `as.data.frame()` additionally appends the metadata columns (`estimate_type`, `group`, `group_level_1`, `group_level_2`, `visit`); the `print()` method still shows only the six classic columns for a compact display.

`mcse()` returns an `mcse` object; a list of class `"mcse"` containing `pars` (the Monte Carlo standard errors of the pooled estimates, in the same structure as the `pars` element of a `pool` object) and `N` (the number of results combined).

References

John Barnard and Donald B. Rubin. Small-Sample Degrees of Freedom with Multiple Imputation. Biometrika, 86(4):948-955, 1999.

Bradley Efron and Robert J Tibshirani. An introduction to the bootstrap. CRC press, 1994. [Section 11]

Bradley Efron and Gail Gong. A leisurely look at the bootstrap, the jackknife, and cross-validation. The American Statistician, 37(1):36-48, 1983.

Roderick J. A. Little and Donald B. Rubin. Statistical Analysis with Missing Data, Second Edition. John Wiley & Sons, Hoboken, New Jersey, 2002. [Section 5.4]

Donald B. Rubin. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons, New York, 1987. [Section 3.3]

Royston, P., Carlin, J. B., & White, I. R. Multiple imputation of missing values: New features for mim. Stata Journal, 9(2): 252-264, 2009.

Von Hippel, Paul T and Bartlett, Jonathan W. Maximum likelihood multiple imputation: Faster imputations and consistent standard errors without posterior draws. 2021.

Examples

```
# Prepare the data: expand to one row per subject and visit
dat <- expand_locf(
    antidepressant_data,
    PATIENT = levels(antidepressant_data$PATIENT),
    VISIT = levels(antidepressant_data$VISIT),
    vars = c("BASVAL", "THERAPY"),
    group = c("PATIENT"),
    order = c("PATIENT", "VISIT")
)

# Derive data_ice: first missing-outcome visit per patient, imputed under JR.
# Subject 3618 has only an intermittent missing value and is removed.
is_missing <- is.na(dat$CHANGE)
dat_ice <- dat[is_missing, c("PATIENT", "VISIT")]
dat_ice <- dat_ice[!duplicated(dat_ice$PATIENT), ]
dat_ice$strategy <- "JR"
dat_ice <- dat_ice[dat_ice$PATIENT != 3618, ]

vars <- set_vars(
    outcome = "CHANGE",
    visit = "VISIT",
    subjid = "PATIENT",
    group = "THERAPY",
    covariates = c("BASVAL*VISIT", "THERAPY*VISIT")
)


# Approximate Bayesian imputation, so that pooling uses Rubin's rules
set.seed(987)
drawObj <- draws(
    data = dat,
    data_ice = dat_ice,
    vars = vars,
    method = method_approxbayes(n_samples = 20),
    quiet = TRUE
)
imputeObj <- impute(
    drawObj,
    references = c("DRUG" = "PLACEBO", "PLACEBO" = "PLACEBO")
)
anaObj <- analyse(
    imputeObj,
    ancova,
    vars = set_vars(
        subjid = "PATIENT",
        outcome = "CHANGE",
        visit = "VISIT",
        group = "THERAPY",
        covariates = "BASVAL"
    )
)
```

```
# Pool the analysis results across the imputed datasets
poolObj <- pool(anaObj)
poolObj

# Monte Carlo standard errors of the pooled estimates
mcse(poolObj, anaObj)
```

`pool_bootstrap_normal` *Bootstrap Pooling via normal approximation*

Description

Get point estimate, confidence interval and p-value using the normal approximation.

Usage

```
pool_bootstrap_normal(est, conf.level, alternative)
```

Arguments

`est`	a numeric vector of point estimates from each bootstrap sample.
`conf.level`	confidence level of the returned confidence interval. Must be a single number between 0 and 1. Default is 0.95.
`alternative`	a character string specifying the alternative hypothesis, must be one of `"two.sided"` (default), `"greater"` or `"less"`.

Details

The point estimate is taken to be the first element of est. The remaining n-1 values of est are then used to generate the confidence intervals.

`pool_bootstrap_percentile`
Bootstrap Pooling via Percentiles

Description

Get point estimate, confidence interval and p-value using percentiles. Note that quantile "type=6" is used, see `stats::quantile()` for details.

Usage

```
pool_bootstrap_percentile(est, conf.level, alternative)
```

Arguments

est	a numeric vector of point estimates from each bootstrap sample.
conf.level	confidence level of the returned confidence interval. Must be a single number between 0 and 1. Default is 0.95.
alternative	a character string specifying the alternative hypothesis, must be one of "two.sided" (default), "greater" or "less".

Details

The point estimate is taken to be the first element of est. The remaining n-1 values of est are then used to generate the confidence intervals.

---

prepare_stan_data *Prepare input data to run the Stan model*

Description

Prepare input data to run the Stan model. Creates / calculates all the required inputs as required by the data{} block of the MMRM Stan program.

Usage

```
prepare_stan_data(ddat, subjid, visit, outcome, group)
```

Arguments

ddat	A design matrix
subjid	Character vector containing the subjects IDs.
visit	Vector containing the visits.
outcome	Numeric vector containing the outcome variable.
group	Vector containing the group variable.

Details

- The group argument determines which covariance matrix group the subject belongs to. If you want all subjects to use a shared covariance matrix then set group to "1" for everyone.

Value

A stan_data object. A named list as per data{} block of the related Stan file. In particular it returns:

- N - The number of rows in the design matrix
- P - The number of columns in the design matrix
- G - The number of distinct covariance matrix groups (i.e. length(unique(group)))

- n_visit - The number of unique outcome visits
- n_pat - The total number of pattern groups (as defined by missingness patterns & covariance group)
- pat_G - Index for which Sigma each pattern group should use
- pat_n_pt - number of patients within each pattern group
- pat_n_visit - number of non-missing visits in each pattern group
- pat_sigma_index - rows/cols from Sigma to subset on for the pattern group (padded by 0's)
- y - The outcome variable
- Q - design matrix (after QR decomposition)
- R - R matrix from the QR decomposition of the design matrix

---

`print.analysis` *Print* `analysis` *object*

Description

Print `analysis` object

Usage

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

Arguments

`x`	An `analysis` object generated by `analyse()`.
`...`	Not used.

`print.draws` *Print* `draws` *object*

Description

Print `draws` object

Usage

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

Arguments

`x`	A `draws` object generated by `draws()`.
`...`	not used.

print.imputation *Print* imputation *object*

Description

Print imputation object

Usage

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

Arguments

x	An imputation object generated by impute().
...	Not used.

progressLogger *R6 Class for printing current sampling progress*

Description

Object is initialised with total number of iterations that are expected to occur. User can then update the object with the add method to indicate how many more iterations have just occurred. Every time step * 100 % of iterations have occurred a message is printed to the console. Use the quiet argument to prevent the object from printing anything at all

Public fields

step real, percentage of iterations to allow before printing the progress to the console

step_current integer, the total number of iterations completed since progress was last printed to the console

n integer, the current number of completed iterations

n_max integer, total number of expected iterations to be completed acts as the denominator for calculating progress percentages

quiet logical holds whether or not to print anything

Methods

Public methods:

- progressLogger$new()
- progressLogger$add()
- progressLogger$print_progress()
- progressLogger$clone()

`progressLogger$new()`: Create `progressLogger` object

Usage:

```
progressLogger$new(n_max, quiet = FALSE, step = 0.1)
```

Arguments:

`n_max` integer, sets field `n_max`

`quiet` logical, sets field `quiet`

`step` real, sets field `step`

`progressLogger$add()`: Records that `n` more iterations have been completed this will add that number to the current step count (`step_current`) and will print a progress message to the log if the step limit (`step`) has been reached. This function will do nothing if `quiet` has been set to `TRUE`

Usage:

```
progressLogger$add(n)
```

Arguments:

`n` the number of successfully complete iterations since `add()` was last called

`progressLogger$print_progress()`: method to print the current state of progress

Usage:

```
progressLogger$print_progress()
```

`progressLogger$clone()`: The objects of this class are cloneable with this method.

Usage:

```
progressLogger$clone(deep = FALSE)
```

Arguments:

`deep` Whether to make a deep clone.

pval_percentile *P-value of percentile bootstrap*

Description

Determines the (not necessarily unique) quantile (type=6) of "est" which gives a value of 0 From this, derive the p-value corresponding to the percentile bootstrap via inversion.

Usage

```
pval_percentile(est)
```

Arguments

`est`	a numeric vector of point estimates from each bootstrap sample.

Details

The p-value for H_0: theta=0 vs H_A: theta>0 is the value `alpha` for which `q_alpha = 0`. If there is at least one estimate equal to zero it returns the largest `alpha` such that `q_alpha = 0`. If all bootstrap estimates are > 0 it returns 0; if all bootstrap estimates are < 0 it returns 1. Analogous reasoning is applied for the p-value for H_0: theta=0 vs H_A: theta<0.

Value

A named numeric vector of length 2 containing the p-value for H_0: theta=0 vs H_A: theta>0 (`"pval_greater"`) and the p-value for H_0: theta=0 vs H_A: theta<0 (`"pval_less"`).

QR_decomp *QR decomposition*

Description

QR decomposition as defined in the Stan user's guide (section 1.2).

Usage

```
QR_decomp(mat)
```

Arguments

`mat`	A matrix to perform the QR decomposition on.

random_effects_expr *Construct random effects formula*

Description

Constructs a character representation of the random effects formula for fitting a MMRM for subject by visit in the format required for `mmrm::mmrm()`.

Usage

```
random_effects_expr(
  cov_struct = c("us", "ad", "adh", "ar1", "ar1h", "cs", "csh", "toep", "toeph"),
  cov_by_group = FALSE
)
```

Arguments

`cov_struct`	Character - The covariance structure to be used, must be one of `"us"` (default), `"ad"`, `"adh"`, `"ar1"`, `"ar1h"`, `"cs"`, `"csh"`, `"toep"`, or `"toeph"`)
`cov_by_group`	Boolean - Whenever or not to use separate covariances per each group level

Details

For example assuming the user specified a covariance structure of "us" and that no groups were provided this will return

```
us(visit | subjid)
```

If `cov_by_group` is set to `FALSE` then this indicates that separate covariance matrices are required per group and as such the following will be returned:

```
us( visit | group / subjid )
```

rbmi-settings *rbmi settings*

Description

Define settings that modify the behaviour of the `rbmi` package

Each of the following are the name of options that can be set via:

```
options(<option_name> = <value>)
```

`rbmi.cache_dir`:

Default = `tempfile()`

Directory to store compiled Stan models in to avoid having to re-compile. If the environment variable `RBMI_CACHE_DIR` has been set this will be used as the default value. Note that if you are running rbmi in multiple R processes at the same time (that is say multiple calls to `Rscript` at once) then there is a theoretical risk of the processes breaking each other as they attempt to read/write to the same cache folder at the same time. To avoid this potential issue it is recommended to leave this value at the default which will result in a unique cache for each process

`rbmi.enable_cache`:

Default = `TRUE`

If `TRUE` then the package will attempt to cache compiled Stan models to the `rbmi.cache_dir` directory. If `FALSE` then the package will re-compile the Stan model each time it is required. If the environment variable `RBMI_ENABLE_CACHE` has been set this will be used as the default value.

Usage

```
set_options()
```

Examples

```
## Not run:
options(rbmi.cache_dir = "some/directory/path")
options(rbmi.enable_cache = FALSE)

## End(Not run)
```

---

record *Capture all Output*

Description

This function silences all warnings, errors & messages and instead returns a list containing the results (if it didn't error) + the warning and error messages as character vectors.

Usage

```
record(expr)
```

Arguments

`expr`	An expression to be executed

Value

A list containing

- **results** - The object returned by `expr` or `list()` if an error was thrown
- **warnings** - NULL or a character vector if warnings were thrown
- **errors** - NULL or a string if an error was thrown
- **messages** - NULL or a character vector if messages were produced

Examples

```
## Not run:
record({
  x <- 1
  y <- 2
  warning("something went wrong")
  message("O nearly done")
  x + y
})

## End(Not run)
```

`recursive_reduce` *recursive_reduce*

Description

Utility function used to replicate `purrr::reduce`. Recursively applies a function to a list of elements until only 1 element remains

Usage

```
recursive_reduce(.l, .f)
```

Arguments

`.l`	list of values to apply a function to
`.f`	function to apply to each each element of the list in turn i.e. `.l[[1]] <- .f( .l[[1]] , .l[[2]]) ; .l[`

remove_if_all_missing *Remove subjects from dataset if they have no observed values*

Description

This function takes a `data.frame` with variables `visit`, `outcome` & `subjid`. It then removes all rows for a given `subjid` if they don't have any non-missing values for `outcome`.

Usage

```
remove_if_all_missing(dat)
```

Arguments

`dat`	a `data.frame`

rubin_df *Barnard and Rubin degrees of freedom adjustment*

Description

Compute degrees of freedom according to the Barnard-Rubin formula.

Usage

```
rubin_df(v_com, var_b, var_t, M)
```

Arguments

`v_com`	Positive number representing the degrees of freedom in the complete-data analysis.
`var_b`	Between-imputation sample variance of the point estimates across multiply imputed datasets.
`var_t`	Estimate (according to Rubin's rules) of the variance of the point estimates.
`M`	Number of imputations (integer larger than 1).

Details

The computation takes into account limit cases where there is no missing data (i.e. the between-variance `var_b` is zero) or where the complete-data degrees of freedom is set to `Inf`. Moreover, if `v_com` is given as `NA`, the function returns `Inf`.

Value

Degrees of freedom according to Barnard-Rubin formula. See Barnard-Rubin (1999).

References

Barnard, J. and Rubin, D.B. (1999). Small sample degrees of freedom with multiple imputation. Biometrika, 86, 948-955.

`rubin_orig_df` *Original Rubin degrees of freedom approximation*

Description

Compute the degrees of freedom according to the original Rubin (1987) approximation.

Usage

```
rubin_orig_df(v_com, var_b, var_t, M)
```

Arguments

`v_com`	Ignored in this function.
`var_b`	Between-imputation sample variance of the point estimates across multiply imputed datasets.
`var_t`	Estimate (according to Rubin's rules) of the variance of the point estimates.
`M`	Number of imputations (integer larger than 1).

Details

Let $V_W = V_T - (1+1/M)V_B$ be the within-imputation variance and $r = (1+1/M)V_B/V_W$ be the relative increase in variance due to nonresponse. The returned degrees of freedom are $(M-1)(1+1/r)^2$. Note that the internal computation is algebraically simplified to $(M-1)((MV_T)/((M+1)V_B))^2$.

Value

Degrees of freedom according to the original Rubin approximation. If the between-imputation variance is zero, returns `Inf`.

References

Rubin, D.B. (1987). Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons, New York. [Section 3.3]

rubin_rules *Combine estimates using Rubin's rules*

Description

Pool together the results from M complete-data analyses according to Rubin's rules. See details.

Usage

```
rubin_rules(ests, ses, v_com, method)
```

Arguments

ests	Numeric vector containing the point estimates from the complete-data analyses.
ses	Numeric vector containing the standard errors from the complete-data analyses.
v_com	Positive number representing the degrees of freedom in the complete-data analysis.
method	Degrees-of-freedom approximation to use: "barnard-rubin" applies the Barnard-Rubin (1999) small-sample adjustment and "rubin" applies Rubin's (1987) original approximation.

Details

rubin_rules applies Rubin's rules (Rubin, 1987) for pooling together the results from a multiple imputation procedure. The pooled point estimate est_point is is the average across the point estimates from the complete-data analyses (given by the input argument ests). The total variance var_t is the sum of two terms representing the within-variance and the between-variance (see Little-Rubin (2002)). The function also returns df, the estimated pooled degrees of freedom according to the selected method, which can be used for inference based on the t-distribution.

Value

A list containing:

- est_point: the pooled point estimate according to Little-Rubin (2002).
- var_t: total variance according to Little-Rubin (2002).
- df: degrees of freedom according to the selected method.

References

Barnard, J. and Rubin, D.B. (1999). Small sample degrees of freedom with multiple imputation. Biometrika, 86, 948-955

Roderick J. A. Little and Donald B. Rubin. Statistical Analysis with Missing Data, Second Edition. John Wiley & Sons, Hoboken, New Jersey, 2002. [Section 5.4]

Rubin, D.B. (1987). Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons, New York. [Section 3.3]

See Also

rubin_df() for the degrees of freedom estimation.

---

sample_ids *Sample Patient Ids*

Description

Performs a stratified bootstrap sample of IDS ensuring the return vector is the same length as the input vector

Usage

```
sample_ids(ids, strata = rep(1, length(ids)))
```

Arguments

ids	vector to sample from
strata	strata indicator, ids are sampled within each strata ensuring the that the numbers of each strata are maintained

Examples

```
## Not run:
sample_ids( c("a", "b", "c", "d"), strata = c(1,1,2,2))

## End(Not run)
```

---

sample_list *Create and validate a* sample_list *object*

Description

Given a list of sample_single objects generate by sample_single(), creates a sample_list objects and validate it.

Usage

```
sample_list(...)
```

Arguments

...	A list of sample_single objects.

sample_mvnorm *Sample random values from the multivariate normal distribution*

Description

Sample random values from the multivariate normal distribution

Usage

```
sample_mvnorm(mu, sigma)
```

Arguments

mu	mean vector
sigma	covariance matrix
	Samples multivariate normal variables by multiplying univariate random normal variables by the Cholesky decomposition of the covariance matrix.
	If mu is length 1 then just uses `rnorm` instead.

sample_single *Create object of* `sample_single` *class*

Description

Creates an object of class `sample_single` which is a named list containing the input parameters and validate them.

Usage

```
sample_single(
  ids,
  beta = NA,
  sigma = NA,
  theta = NA,
  failed = any(is.na(beta)),
  ids_samp = ids
)
```

Arguments

ids	Vector of characters containing the ids of the subjects included in the original dataset.
beta	Numeric vector of estimated regression coefficients.
sigma	List of estimated covariance matrices (one for each level of `vars$group`).

theta	Numeric vector of transformed covariances.
failed	Logical. TRUE if the model fit failed.
ids_samp	Vector of characters containing the ids of the subjects included in the given sample.

Value

A named list of class sample_single. It contains the following:

- ids vector of characters containing the ids of the subjects included in the original dataset.
- beta numeric vector of estimated regression coefficients.
- sigma list of estimated covariance matrices (one for each level of vars$group).
- theta numeric vector of transformed covariances.
- failed logical. TRUE if the model fit failed.
- ids_samp vector of characters containing the ids of the subjects included in the given sample.

---

scalerConstructor *R6 Class for scaling (and un-scaling) design matrices*

Description

Scales a design matrix so that all non-categorical columns have a mean of 0 and an standard deviation of 1.

Details

The object initialisation is used to determine the relevant means and standard deviations to scale by and then the scaling (and un-scaling) itself is performed by the relevant object methods.

Un-scaling is done on linear model Beta and Sigma coefficients. For this purpose the first column on the dataset to be scaled is assumed to be the outcome variable with all other variables assumed to be post-transformation predictor variables (i.e. all dummy variables have already been expanded).

Public fields

centre Vector of column means. The first value is the outcome variable, all other variables are the predictors.

scales Vector of column standard deviations. The first value is the outcome variable, all other variables are the predictors.

Methods

Public methods:

- scaler$new()
- scaler$scale()
- scaler$unscale_sigma()
- scaler$unscale_beta()
- scaler$clone()

`scaler$new()`: Uses `dat` to determine the relevant column means and standard deviations to use when scaling and un-scaling future datasets. Implicitly assumes that new datasets have the same column order as `dat`

Usage:

```
scaler$new(dat)
```

Arguments:

`dat` A `data.frame` or matrix. All columns must be numeric (i.e dummy variables, must have already been expanded out).

Details: Categorical columns (as determined by those who's values are entirely `1` or `0`) will not be scaled. This is achieved by setting the corresponding values of centre to `0` and scale to `1`.

`scaler$scale()`: Scales a dataset so that all continuous variables have a mean of 0 and a standard deviation of 1.

Usage:

```
scaler$scale(dat)
```

Arguments:

`dat` A `data.frame` or matrix whose columns are all numeric (i.e. dummy variables have all been expanded out) and whose columns are in the same order as the dataset used in the initialization function.

`scaler$unscale_sigma()`: Unscales a sigma value (or matrix) as estimated by a linear model using a design matrix scaled by this object. This function only works if the first column of the initialisation `data.frame` was the outcome variable.

Usage:

```
scaler$unscale_sigma(sigma)
```

Arguments:

`sigma` A numeric value or matrix.

Returns: A numeric value or matrix

`scaler$unscale_beta()`: Unscales a beta value (or vector) as estimated by a linear model using a design matrix scaled by this object. This function only works if the first column of the initialization `data.frame` was the outcome variable.

Usage:

```
scaler$unscale_beta(beta)
```

Arguments:

`beta` A numeric vector of beta coefficients as estimated from a linear model.

Returns: A numeric vector.

`scaler$clone()`: The objects of this class are cloneable with this method.

Usage:

```
scaler$clone(deep = FALSE)
```

Arguments:

`deep` Whether to make a deep clone.

`set_simul_pars` *Set simulation parameters of a study group.*

Description

This function provides input arguments for each study group needed to simulate data with `simulate_data()`. `simulate_data()` generates data for a two-arms clinical trial with longitudinal continuous outcomes and two intercurrent events (ICEs). ICE1 may be thought of as a discontinuation from study treatment due to study drug or condition related (SDCR) reasons. ICE2 may be thought of as discontinuation from study treatment due to uninformative study drop-out, i.e. due to not study drug or condition related (NSDCR) reasons and outcome data after ICE2 is always missing.

Usage

```
set_simul_pars(
  mu,
  sigma,
  n,
  prob_ice1 = 0,
  or_outcome_ice1 = 1,
  prob_post_ice1_dropout = 0,
  prob_ice2 = 0,
  prob_miss = 0
)
```

Arguments

`mu`	Numeric vector describing the mean outcome trajectory at each visit (including baseline) assuming no ICEs.
`sigma`	Covariance matrix of the outcome trajectory assuming no ICEs.
`n`	Number of subjects belonging to the group.
`prob_ice1`	Numeric vector that specifies the probability of experiencing ICE1 (discontinuation from study treatment due to SDCR reasons) after each visit for a subject with observed outcome at that visit equal to the mean at baseline (`mu[1]`). If a single numeric is provided, then the same probability is applied to each visit.

or_outcome_ice1
: Numeric value that specifies the odds ratio of experiencing ICE1 after each visit corresponding to a +1 higher value of the observed outcome at that visit.

prob_post_ice1_dropout
: Numeric value that specifies the probability of study drop-out following ICE1. If a subject is simulated to drop-out after ICE1, all outcomes after ICE1 are set to missing.

prob_ice2
: Numeric that specifies an additional probability that a post-baseline visit is affected by study drop-out. Outcome data at the subject's first simulated visit affected by study drop-out and all subsequent visits are set to missing. This generates a second intercurrent event ICE2, which may be thought as treatment discontinuation due to NSDCR reasons with subsequent drop-out. If for a subject, both ICE1 and ICE2 are simulated to occur, then it is assumed that only the earlier of them counts. In case both ICEs are simulated to occur at the same time, it is assumed that ICE1 counts. This means that a single subject can experience either ICE1 or ICE2, but not both of them.

prob_miss
: Numeric value that specifies an additional probability for a given post-baseline observation to be missing. This can be used to produce "intermittent" missing values which are not associated with any ICE.

Details

For the details, please see `simulate_data()`.

Value

A `simul_pars` object which is a named list containing the simulation parameters.

See Also

`simulate_data()`

Examples

```
# Simulation parameters for a group with 5 visits (including baseline)
time <- c(0, 3, 6, 9, 12)

# Mean outcome trajectory
mu <- c(50.0, 52.5, 55.0, 57.5, 60.0)

# Covariance matrix implied by a random intercept and slope model
sd_error <- 2.5
covRE <- rbind(
    c(25.0, 6.25),
    c(6.25, 25.0)
)
sigma <- cbind(1, time / 12) %*% covRE %*% rbind(1, time / 12) +
    diag(sd_error^2, nrow = length(time))

set_simul_pars(
```

```
    mu = mu,
    sigma = sigma,
    n = 100,
    prob_ice1 = 0.03,
    or_outcome_ice1 = 1.10,
    prob_post_ice1_dropout = 0.5
)
```

`set_vars` *Set key variables*

Description

This function is used to define the names of key variables within the `data.frame`'s that are provided as input arguments to `draws()` and `ancova()`.

Usage

```
set_vars(
  subjid = "subjid",
  visit = "visit",
  outcome = "outcome",
  group = "group",
  covariates = character(0),
  strata = group,
  strategy = "strategy",
  group_contrasts = NULL
)
```

Arguments

`subjid`	The name of the "Subject ID" variable. A length 1 character vector.
`visit`	The name of the "Visit" variable. A length 1 character vector.
`outcome`	The name of the "Outcome" variable. A length 1 character vector.
`group`	The name of the "Group" variable. A length 1 character vector.
`covariates`	The name of any covariates to be used in the context of modelling. See details.
`strata`	The name of the any stratification variable to be used in the context of bootstrap sampling. See details.
`strategy`	The name of the "strategy" variable. A length 1 character vector.
`group_contrasts`	Optional specification of the treatment-group contrasts to be estimated by `ancova()`. Either `NULL` (the default) or a fully named list whose elements are one of: • a length-2 character vector `c(minuend, subtrahend)` giving a pairwise contrast `minuend - subtrahend` between two levels of `group`; or

- a numeric weight vector over the group levels (summing to zero), either named by the levels of group (unlisted levels default to 0) or of the same length as the number of levels (in factor order).

Each element must be named; the name is used as the output parameter name (and must not start with lsm_, which is reserved for the least-squares means). See details.

Details

In both draws() and ancova() the covariates argument can be specified to indicate which variables should be included in the imputation and analysis models respectively. If you wish to include interaction terms these need to be manually specified i.e. covariates = c("group*visit", "age*sex"). Please note that the use of the I() function to inhibit the interpretation/conversion of objects is not supported.

The group_contrasts argument is only used by ancova(). If NULL (default) a treatment effect is estimated for every non-reference group versus the reference group (the first factor level of group). Alternatively a bespoke set of contrasts can be requested. Pairwise contrasts are given as length-2 character vectors, e.g. group_contrasts = list(c("A", "Placebo"), c("B", "Placebo")) requests the contrasts A - Placebo and B - Placebo. More general linear contrasts are given as named numeric weight vectors over the group levels, e.g. group_contrasts = list(pooled_vs_pbo = c(Placebo = -1, A = 0.5, B = 0.5)) contrasts the average of A and B against Placebo. List names are carried through to the contrast_label column of the pool() output; weight-vector contrasts must be named. See ancova() for the resulting parameter naming scheme.

Currently strata is only used by draws() in combination with method_condmean(type = "bootstrap") and method_approxbayes() in order to allow for the specification of stratified bootstrap sampling. By default strata is set equal to the value of group as it is assumed most users will want to preserve the group size between samples. See draws() for more details.

Likewise, currently the strategy argument is only used by draws() to specify the name of the strategy variable within the data_ice data.frame. See draws() for more details.

Value

A vars object; a named list of class ivars recording the names of the key variables (subjid, visit, outcome, group, covariates, strata and strategy) used throughout rbmi by functions such as draws(), ancova() and analyse().

See Also

draws()

ancova()

Examples

```
## Not run:

# Using CDISC variable names as an example
set_vars(
    subjid = "usubjid",
```

```
    visit = "avisit",
    outcome = "aval",
    group = "arm",
    covariates = c("bwt", "bht", "arm * avisit"),
    strategy = "strat"
)


## End(Not run)
```

`simulate_data` *Generate data*

Description

Generate data for a two-arms clinical trial with longitudinal continuous outcome and two intercurrent events (ICEs). ICE1 may be thought of as a discontinuation from study treatment due to study drug or condition related (SDCR) reasons. ICE2 may be thought of as discontinuation from study treatment due to uninformative study drop-out, i.e. due to not study drug or condition related (NSDCR) reasons and outcome data after ICE2 is always missing.

Usage

```
simulate_data(pars_c, pars_t, post_ice1_traj, strategies = getStrategies())
```

Arguments

`pars_c`	A `simul_pars` object as generated by `set_simul_pars()`. It specifies the simulation parameters of the control arm.
`pars_t`	A `simul_pars` object as generated by `set_simul_pars()`. It specifies the simulation parameters of the treatment arm.
`post_ice1_traj`	A string which specifies how observed outcomes occurring after ICE1 are simulated. Must target a function included in `strategies`. Possible choices are: Missing At Random `"MAR"`, Jump to Reference `"JR"`, Copy Reference `"CR"`, Copy Increments in Reference `"CIR"`, Last Mean Carried Forward `"LMCF"`. User-defined strategies could also be added. See `getStrategies()` for details.
`strategies`	A named list of functions. Default equal to `getStrategies()`. See `getStrategies()` for details.

Details

The data generation works as follows:

- Generate outcome data for all visits (including baseline) from a multivariate normal distribution with parameters `pars_c$mu` and `pars_c$sigma` for the control arm and parameters `pars_t$mu` and `pars_t$sigma` for the treatment arm, respectively. Note that for a randomized trial, outcomes have the same distribution at baseline in both treatment groups, i.e. one should set `pars_c$mu[1]=pars_t$mu[1]` and `pars_c$sigma[1,1]=pars_t$sigma[1,1]`.

- Simulate whether ICE1 (study treatment discontinuation due to SDCR reasons) occurs after each visit according to parameters pars_c$prob_ice1 and pars_c$or_outcome_ice1 for the control arm and pars_t$prob_ice1 and pars_t$or_outcome_ice1 for the treatment arm, respectively.
- Simulate drop-out following ICE1 according to pars_c$prob_post_ice1_dropout and pars_t$prob_post_ice1_dro
- Simulate an additional uninformative study drop-out with probabilities pars_c$prob_ice2 and pars_t$prob_ice2 at each visit. This generates a second intercurrent event ICE2, which may be thought as treatment discontinuation due to NSDCR reasons with subsequent drop-out. The simulated time of drop-out is the subject's first visit which is affected by drop-out and data from this visit and all subsequent visits are consequently set to missing. If for a subject, both ICE1 and ICE2 are simulated to occur, then it is assumed that only the earlier of them counts. In case both ICEs are simulated to occur at the same time, it is assumed that ICE1 counts. This means that a single subject can experience either ICE1 or ICE2, but not both of them.
- Adjust trajectories after ICE1 according to the given assumption expressed with the post_ice1_traj argument. Note that only post-ICE1 outcomes in the intervention arm can be adjusted. Post-ICE1 outcomes from the control arm are not adjusted.
- Simulate additional intermittent missing outcome data as per arguments pars_c$prob_miss and pars_t$prob_miss.

The probability of the ICE after each visit is modelled according to the following logistic regression model: ~ 1 + I(visit == 0) + ... + I(visit == n_visits-1) + I((x-alpha)) where:

- n_visits is the number of visits (including baseline).
- alpha is the baseline outcome mean. The term I((x-alpha)) specifies the dependency of the probability of the ICE on the current outcome value. The corresponding regression coefficients of the logistic model are defined as follows: The intercept is set to 0, the coefficients corresponding to discontinuation after each visit for a subject with outcome equal to the mean at baseline are set according to parameters pars_c$prob_ice1 (pars_t$prob_ice1), and the regression coefficient associated with the covariate I((x-alpha)) is set to log(pars_c$or_outcome_ice1) (log(pars_t$or_outcome_ice1)).

Please note that the baseline outcome cannot be missing nor be affected by any ICEs.

Value

A data.frame containing the simulated data. It includes the following variables:

- id: Factor variable that specifies the id of each subject.
- visit: Factor variable that specifies the visit of each assessment. Visit 0 denotes the baseline visit.
- group: Factor variable that specifies which treatment group each subject belongs to.
- outcome_bl: Numeric variable that specifies the baseline outcome.
- outcome_noICE: Numeric variable that specifies the longitudinal outcome assuming no ICEs.
- ind_ice1: Binary variable that takes value 1 if the corresponding visit is affected by ICE1 and 0 otherwise.

- `dropout_ice1`: Binary variable that takes value `1` if the corresponding visit is affected by the drop-out following ICE1 and `0` otherwise.
- `ind_ice2`: Binary variable that takes value `1` if the corresponding visit is affected by ICE2.
- `outcome`: Numeric variable that specifies the longitudinal outcome including ICE1, ICE2 and the intermittent missing values.

Examples

```
set.seed(1392)

time <- c(0, 3, 6, 9, 12)

# Mean outcome trajectory in the control and intervention groups
muC <- c(50.0, 52.5, 55.0, 57.5, 60.0)
muT <- c(50.0, 52.5, 55.0, 56.25, 57.50)

# Covariance matrix implied by a random intercept and slope model
sd_error <- 2.5
covRE <- rbind(
    c(25.0, 6.25),
    c(6.25, 25.0)
)
Sigma <- cbind(1, time / 12) %*% covRE %*% rbind(1, time / 12) +
    diag(sd_error^2, nrow = length(time))

# Simulation parameters of the control group
parsC <- set_simul_pars(
    mu = muC,
    sigma = Sigma,
    n = 100,
    prob_ice1 = 0.03,
    or_outcome_ice1 = 1.10,
    prob_post_ice1_dropout = 0.5
)

# Simulation parameters of the intervention group
parsT <- parsC
parsT$mu <- muT
parsT$prob_ice1 <- 0.04

# Simulate a dataset with a copy-increments-in-reference post-ICE1 trajectory
data <- simulate_data(
    pars_c = parsC,
    pars_t = parsT,
    post_ice1_traj = "CIR"
)
head(data)
```

simulate_dropout *Simulate drop-out*

Description

Simulate drop-out

Usage

```
simulate_dropout(prob_dropout, ids, subset = rep(1, length(ids)))
```

Arguments

prob_dropout	Numeric that specifies the probability that a post-baseline visit is affected by study drop-out.
ids	Factor variable that specifies the id of each subject.
subset	Binary variable that specifies the subset that could be affected by drop-out. I.e. subset is a binary vector of length equal to the length of ids that takes value 1 if the corresponding visit could be affected by drop-out and 0 otherwise.

Details

subset can be used to specify outcome values that cannot be affected by the drop-out. By default subset will be set to 1 for all the values except the values corresponding to the baseline outcome, since baseline is supposed to not be affected by drop-out. Even if subset is specified by the user, the values corresponding to the baseline outcome are still hard-coded to be 0.

Value

A binary vector of length equal to the length of ids that takes value 1 if the corresponding outcome is affected by study drop-out.

simulate_ice *Simulate intercurrent event*

Description

Simulate intercurrent event

Usage

```
simulate_ice(outcome, visits, ids, prob_ice, or_outcome_ice, baseline_mean)
```

Arguments

outcome	Numeric variable that specifies the longitudinal outcome for a single group.
visits	Factor variable that specifies the visit of each assessment.
ids	Factor variable that specifies the id of each subject.
prob_ice	Numeric vector that specifies for each visit the probability of experiencing the ICE after the current visit for a subject with outcome equal to the mean at baseline. If a single numeric is provided, then the same probability is applied to each visit.
or_outcome_ice	Numeric value that specifies the odds ratio of the ICE corresponding to a +1 higher value of the outcome at the visit.
baseline_mean	Mean outcome value at baseline.

Details

The probability of the ICE after each visit is modelled according to the following logistic regression model: `~ 1 + I(visit == 0) + ... + I(visit == n_visits-1) + I((x-alpha))` where:

- `n_visits` is the number of visits (including baseline).
- `alpha` is the baseline outcome mean set via argument `baseline_mean`. The term `I((x-alpha))` specifies the dependency of the probability of the ICE on the current outcome value. The corresponding regression coefficients of the logistic model are defined as follows: The intercept is set to 0, the coefficients corresponding to discontinuation after each visit for a subject with outcome equal to the mean at baseline are set according to parameter `or_outcome_ice`, and the regression coefficient associated with the covariate `I((x-alpha))` is set to `log(or_outcome_ice)`.

Value

A binary variable that takes value `1` if the corresponding outcome is affected by the ICE and `0` otherwise.

`simulate_test_data` *Create simulated datasets*

Description

Creates a longitudinal dataset in the format that `rbmi` was designed to analyse.

Usage

```
simulate_test_data(
  n = 200,
  sd = c(3, 5, 7),
  cor = c(0.1, 0.7, 0.4),
  mu = list(int = 10, age = 3, sex = 2, trt = c(0, 4, 8), visit = c(0, 1, 2))
)

as_vcov(sd, cor)
```

Arguments

n	the number of subjects to sample. Total number of observations returned is thus n * length(sd)
sd	the standard deviations for the outcome at each visit. i.e. the square root of the diagonal of the covariance matrix for the outcome
cor	the correlation coefficients between the outcome values at each visit. See details.
mu	the coefficients to use to construct the mean outcome value at each visit. Must be a named list with elements int, age, sex, trt & visit. See details.

Details

The number of visits is determined by the size of the variance covariance matrix. i.e. if 3 standard deviation values are provided then 3 visits per patient will be created.

The covariates in the simulated dataset are produced as follows:

- Patients age is sampled at random from a N(0,1) distribution
- Patients sex is sampled at random with a 50/50 split
- Patients group is sampled at random but fixed so that each group has n/2 patients
- The outcome variable is sampled from a multivariate normal distribution, see below for details

The mean for the outcome variable is derived as:

```
outcome = Intercept + age + sex + visit + treatment
```

The coefficients for the intercept, age and sex are taken from muint, muage and mu$sex respectively, all of which must be a length 1 numeric.

Treatment and visit coefficients are taken from mu$trt and mu$visit respectively and must either be of length 1 (i.e. a constant affect across all visits) or equal to the number of visits (as determined by the length of sd). I.e. if you wanted a treatment slope of 5 and a visit slope of 1 you could specify:

```
mu = list(..., "trt" = c(0,5,10), "visit" = c(0,1,2))
```

The correlation matrix is constructed from cor as follows. Let cor = c(a, b, c, d, e, f) then the correlation matrix would be:

```
1  a  b  d
a  1  c  e
b  c  1  f
d  e  f  1
```

Value

as_vcov() returns a symmetric positive-definite covariance matrix (a numeric matrix) constructed from the vector of standard deviations sd and the correlation entries cor.

Examples

```
# Construct a 3x3 covariance matrix from standard deviations and correlations.
# `cor` gives the upper-triangular correlations in row-major order:
# cor(1,2), cor(1,3), cor(2,3).
as_vcov(
    sd = c(1, 3, 2),
    cor = c(0.4, 0.5, 0.45)
)
```

---

sort_by *Sort* data.frame

Description

Sorts a data.frame (ascending by default) based upon variables within the dataset

Usage

```
sort_by(df, vars = NULL, decreasing = FALSE)
```

Arguments

df	data.frame
vars	character vector of variables
decreasing	logical whether sort order should be in descending or ascending (default) order. Can be either a single logical value (in which case it is applied to all variables) or a vector which is the same length as vars

Examples

```
## Not run:
sort_by(iris, c("Sepal.Length", "Sepal.Width"), decreasing = c(TRUE, FALSE))

## End(Not run)
```

---

split_dim *Transform array into list of arrays*

Description

Transform an array into list of arrays where the listing is performed on a given dimension.

Usage

```
split_dim(a, n)
```

Arguments

a	Array with number of dimensions at least 2.
n	Positive integer. Dimension of a to be listed.

Details

For example, if a is a 3 dimensional array and n = 1, split_dim(a,n) returns a list of 2 dimensional arrays (i.e. a list of matrices) where each element of the list is a[i, ,], where i takes values from 1 to the length of the first dimension of the array.

Example:

inputs: a <- array(c(1,2,3,4,5,6,7,8,9,10,11,12), dim = c(3,2,2)), which means that:

```
a[1,,]     a[2,,]     a[3,,]

[,1] [,2]  [,1] [,2]  [,1] [,2]
---------  ---------  ---------
 1    7     2    8     3    9
 4    10    5    11    6    12
```

n <- 1

output of res <- split_dim(a,n) is a list of 3 elements:

```
res[[1]]   res[[2]]   res[[3]]

[,1] [,2]  [,1] [,2]  [,1] [,2]
---------  ---------  ---------
 1    7     2    8     3    9
 4    10    5    11    6    12
```

Value

A list of length n of arrays with number of dimensions equal to the number of dimensions of a minus 1.

---

split_imputations *Split a flat list of imputation_single() into multiple imputation_df()'s by ID*

Description

Split a flat list of imputation_single() into multiple imputation_df()'s by ID

Usage

```
split_imputations(list_of_singles, split_ids)
```

Arguments

list_of_singles	A list of imputation_single()'s
split_ids	A list with 1 element per required split. Each element must contain a vector of "ID"'s which correspond to the imputation_single() ID's that are required within that sample. The total number of ID's must by equal to the length of list_of_singles

Details

This function converts a list of imputations from being structured per patient to being structured per sample i.e. it converts

```
obj <- list(
    imputation_single("Ben", numeric(0)),
    imputation_single("Ben", numeric(0)),
    imputation_single("Ben", numeric(0)),
    imputation_single("Harry", c(1, 2)),
    imputation_single("Phil", c(3, 4)),
    imputation_single("Phil", c(5, 6)),
    imputation_single("Tom", c(7, 8, 9))
)

index <- list(
    c("Ben", "Harry", "Phil", "Tom"),
    c("Ben", "Ben", "Phil")
)
```

Into:

```
output <- list(
    imputation_df(
        imputation_single(id = "Ben", values = numeric(0)),
        imputation_single(id = "Harry", values = c(1, 2)),
        imputation_single(id = "Phil", values = c(3, 4)),
        imputation_single(id = "Tom", values = c(7, 8, 9))
    ),
    imputation_df(
        imputation_single(id = "Ben", values = numeric(0)),
        imputation_single(id = "Ben", values = numeric(0)),
        imputation_single(id = "Phil", values = c(5, 6))
    )
)
```

STAN_BLOCKS *List of Stan Blocks*

Description

A list with 1 element per standard Stan program blocks. This object is mostly used internally as a reference for what blocks are parsed from a covariance / prior Stan definition file.

Usage

```
STAN_BLOCKS
```

str_contains *Does a string contain a substring*

Description

Returns a vector of TRUE/FALSE for each element of x if it contains any element in subs

i.e.

```
str_contains( c("ben", "tom", "harry"), c("e", "y"))
[1] TRUE FALSE TRUE
```

Usage

```
str_contains(x, subs)
```

Arguments

x	character vector
subs	a character vector of substrings to look for

`strategies` *Strategies*

Description

These functions are used to implement various reference based imputation strategies by combining a subjects own distribution with that of a reference distribution based upon which of their visits failed to meet the Missing-at-Random (MAR) assumption.

Usage

```
strategy_MAR(pars_group, pars_ref, index_mar)

strategy_JR(pars_group, pars_ref, index_mar)

strategy_CR(pars_group, pars_ref, index_mar)

strategy_CIR(pars_group, pars_ref, index_mar)

strategy_LMCF(pars_group, pars_ref, index_mar)
```

Arguments

`pars_group`	A list of parameters for the subject's group. See details.
`pars_ref`	A list of parameters for the subject's reference group. See details.
`index_mar`	A logical vector indicating which visits meet the MAR assumption for the subject. I.e. this identifies the observations after a non-MAR intercurrent event (ICE).

Details

`pars_group` and `pars_ref` both must be a list containing elements `mu` and `sigma`. `mu` must be a numeric vector and `sigma` must be a square matrix symmetric covariance matrix with dimensions equal to the length of `mu` and `index_mar`. e.g.

```
list(
    mu = c(1,2,3),
    sigma = matrix(c(4,3,2,3,5,4,2,4,6), nrow = 3, ncol = 3)
)
```

Users can define their own strategy functions and include them via the `strategies` argument to `impute()` using `getStrategies()`. That being said the following strategies are available "out the box":

- Missing at Random (MAR)
- Jump to Reference (JR)

- Copy Reference (CR)
- Copy Increments in Reference (CIR)
- Last Mean Carried Forward (LMCF)

Value

A list with elements `mu` (a numeric vector of means) and `sigma` (a covariance matrix) giving the parameters of the subject's imputation distribution, formed by combining their own group's parameters (`pars_group`) with the reference group's parameters (`pars_ref`) according to the chosen strategy.

Examples

```
# Parameters of the subject's own group and of the reference group
pars_group <- list(
    mu = c(1, 2, 3),
    sigma = as_vcov(c(1, 3, 2), c(0.4, 0.5, 0.45))
)
pars_ref <- list(
    mu = c(5, 6, 7),
    sigma = as_vcov(c(2, 1, 1), c(0.7, 0.8, 0.5))
)

# The first two visits meet the MAR assumption, the third does not
index_mar <- c(TRUE, TRUE, FALSE)

# Combine the parameters according to the different strategies
strategy_MAR(pars_group, pars_ref, index_mar)
strategy_JR(pars_group, pars_ref, index_mar)
strategy_CR(pars_group, pars_ref, index_mar)
strategy_CIR(pars_group, pars_ref, index_mar)
strategy_LMCF(pars_group, pars_ref, index_mar)
```

`string_pad` *string_pad*

Description

Utility function used to replicate `str_pad`. Adds white space to either end of a string to get it to equal the desired length

Usage

```
string_pad(x, width)
```

Arguments

`x`	string
`width`	desired length

transpose_imputations *Transpose imputations*

Description

Takes an imputation_df object and transposes it e.g.

```
list(
    list(id = "a", values = c(1,2,3)),
    list(id = "b", values = c(4,5,6)
    )
)
```

Usage

```
transpose_imputations(imputations)
```

Arguments

imputations	An imputation_df object created by imputation_df()

Details

becomes

```
list(
    ids = c("a", "b"),
    values = c(1,2,3,4,5,6)
)
```

transpose_results *Transpose results object*

Description

Transposes a Results object (as created by analyse()) in order to group the same estimates together into vectors.

Usage

```
transpose_results(results, components)
```

Arguments

results	A list of results.
components	a character vector of components to extract (i.e. "est", "se").

Details

Essentially this function takes an object of the format:

```
x <- list(
    list(
        "trt1" = list(
            est = 1,
            se  = 2
        ),
        "trt2" = list(
            est = 3,
            se  = 4
        )
    ),
    list(
        "trt1" = list(
            est = 5,
            se  = 6
        ),
        "trt2" = list(
            est = 7,
            se  = 8
        )
    )
)
```

and produces:

```
list(
    trt1 = list(
        est = c(1,5),
        se = c(2,6)
    ),
    trt2 = list(
        est = c(3,7),
        se = c(4,8)
    )
)
```

`transpose_samples` *Transpose samples*

Description

Transposes samples generated by `draws()` so that they are grouped by `subjid` instead of by sample number.

Usage

```
transpose_samples(samples)
```

Arguments

samples	A list of samples generated by draws().

---

validate.analysis *Validate* analysis *objects*

Description

Validates the return object of the analyse() function.

Usage

```
## S3 method for class 'analysis'
validate(x, ...)
```

Arguments

x	An analysis results object (of class "jackknife", "bootstrap", "rubin").
...	Not used.

---

validate.draws *Validate* draws *object*

Description

Validate draws object

Usage

```
## S3 method for class 'draws'
validate(x, ...)
```

Arguments

x	A draws object generated by as_draws().
...	Not used.

validate.is_mar *Validate* is_mar *for a given subject*

Description

Checks that the longitudinal data for a patient is divided in MAR followed by non-MAR data; a non-MAR observation followed by a MAR observation is not allowed.

Usage

```
## S3 method for class 'is_mar'
validate(x, ...)
```

Arguments

x	Object of class is_mar. Logical vector indicating whether observations are MAR.
...	Not used.

Value

Will error if there is an issue otherwise will return TRUE.

validate.ivars *Validate inputs for* vars

Description

Checks that the required variable names are defined within vars and are of appropriate data types

Usage

```
## S3 method for class 'ivars'
validate(x, ...)
```

Arguments

x	named list indicating the names of key variables in the source dataset
...	not used

validate.references *Validate user supplied references*

Description

Checks to ensure that the user specified references are expect values (i.e. those found within the source data).

Usage

```
## S3 method for class 'references'
validate(x, control, ...)
```

Arguments

x	named character vector.
control	factor variable (should be the group variable from the source dataset).
...	Not used.

Value

Will error if there is an issue otherwise will return TRUE.

validate.sample_list *Validate* sample_list *object*

Description

Validate sample_list object

Usage

```
## S3 method for class 'sample_list'
validate(x, ...)
```

Arguments

x	A sample_list object generated by sample_list().
...	Not used.

validate.sample_single *Validate* sample_single *object*

Description

Validate sample_single object

Usage

```
## S3 method for class 'sample_single'
validate(x, ...)
```

Arguments

x	A sample_single object generated by sample_single().
...	Not used.

validate.simul_pars *Validate a* simul_pars *object*

Description

Validate a simul_pars object

Usage

```
## S3 method for class 'simul_pars'
validate(x, ...)
```

Arguments

x	An simul_pars object as generated by set_simul_pars().
...	Not used.

validate.stan_data *Validate a* stan_data *object*

Description

Validate a stan_data object

Usage

```
## S3 method for class 'stan_data'
validate(x, ...)
```

Arguments

x	A stan_data object.
...	Not used.

validate_datalong *Validate a* longdata *object*

Description

Validate a longdata object

Usage

```
validate_datalong(data, vars)

validate_datalong_varExists(data, vars)

validate_datalong_types(data, vars)

validate_datalong_notMissing(data, vars)

validate_datalong_complete(data, vars)

validate_datalong_unifromStrata(data, vars)

validate_dataice(data, data_ice, vars, update = FALSE)
```

Arguments

data	a data.frame containing the longitudinal outcome data + covariates for multiple subjects
vars	a vars object as created by set_vars()
data_ice	a data.frame containing the subjects ICE data. See draws() for details.
update	logical, indicates if the ICE data is being set for the first time or if an update is being applied

Details

These functions are used to validate various different parts of the longdata object to be used in draws(), impute(), analyse() and pool(). In particular:

- validate_datalong_varExists - Checks that each variable listed in vars actually exists in the data
- validate_datalong_types - Checks that the types of each key variable is as expected i.e. that visit is a factor variable
- validate_datalong_notMissing - Checks that none of the key variables (except the outcome variable) contain any missing values
- validate_datalong_complete - Checks that data is complete i.e. there is 1 row for each subject * visit combination. e.g. that nrow(data) == length(unique(subjects)) * length(unique(visits))
- validate_datalong_unifromStrata - Checks to make sure that any variables listed as stratification variables do not vary over time. e.g. that subjects don't switch between stratification groups.

---

validate_strategies *Validate user specified strategies*

Description

Compares the user provided strategies to those that are required (the reference). Will throw an error if not all values of reference have been defined.

Usage

```
validate_strategies(strategies, reference)
```

Arguments

strategies	named list of strategies.
reference	list or character vector of strategies that need to be defined.

Value

Will throw an error if there is an issue otherwise will return TRUE.

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