

Package: ballast (via r-universe)

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Title Stress-Test a Pre-Specified Mixed Model for Repeated Measures

Version 0.6.1

Description Refits one pre-specified mixed model for repeated measures (MMRM) under families of data and analytic perturbations (covariance structure, degrees-of-freedom method and variance estimator, covariate set, analysis population, alternative analysis data sets, leave-one-out deletions, crossed specification grids, re-randomisation tests, delta-adjusted and reference-based multiple imputation, and alternative estimators) and judges every refit against the pre-specified estimate, confidence interval and p-value. Classifies the result as robust, sensitive or fragile, with a separate flag for marginal significance, and estimates by simulation the probability that a planned design gives a significant and robust result. Fitting uses 'mmrm' (Sabanés Bove et al., 2024, <<https://openpharma.github.io/mmrm/>>) with 'SAS' 'PROC MIXED' conventions for the least-squares-mean contrast, Kenward-Roger adjustment and the corrected Akaike criterion. Reference-based multiple imputation follows Carpenter, Roger and Kenward (2013) <[doi:10.1080/10543406.2013.834911](https://doi.org/10.1080/10543406.2013.834911)> and was checked against 'rbmi' (Gower-Page, Noci and Wolbers, 2022) <[doi:10.21105/joss.04251](https://doi.org/10.21105/joss.04251)>.

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default_inference	Default inference settings for stress_inference()
-------------------	---

Description

Default inference settings for [stress_inference\(\)](#)

Usage

`default_inference()`

Value

A named list of `list(method = , vcov = )` pairs: Satterthwaite, Kenward-Roger, linear Kenward-Roger (the SAS DDFM=KR default), residual, sandwich with between-within degrees of freedom (SAS EMPIRICAL) and the jackknife sandwich.

Examples

`names(default_inference())`

mask_ids	<i>Mask subject identifiers in a census</i>
----------	---

Description

Replaces subject identifiers in the labels of the leave-one-subject-out and deletion-search rows with sequence numbers (S001, S002, ...) in the order of the spec's subject levels, so that a census, report or page can leave the organisation without participant identifiers. The mapping is returned as `attr(, "id_map")`.

Usage

```
mask_ids(census, spec)
```

Arguments

census	A stress_census (or stress_rows).
spec	The stress_spec() the census was built from.

Value

The same object with masked labels.

Examples

```
small <- mrmr::fev_data[mrmr::fev_data$USUBJID %in% paste0("PT", 1:40), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
cen <- stress_census(spec, stress_loo(spec))
head(mask_ids(cen, spec)$label)
```

plot.stress_census	<i>Plot a census: one row per family on the percent-of-base axis</i>
--------------------	--

Description

Each counted analysis is a point at its estimate as a percent of the base estimate, filled by significance; the shaded band is the base confidence interval on the same axis and the vertical line is the base estimate. Deletions are drawn in a separate panel from alternative analyses.

Usage

```
## S3 method for class 'stress_census'
plot(x, ...)
```

Arguments

x A stress_census.
 ... Unused.

Value

A ggplot object.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:80), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
cen <- stress_census(spec, stress_covariance(spec, c("cs", "ar1h")),
  stress_loo(spec, by = "RACE"))
if (requireNamespace("ggplot2", quietly = TRUE)) plot(cen)
```

plot.stress_design	<i>Plot power and robustness power against the sample size</i>
--------------------	--

Description

Plot power and robustness power against the sample size

Usage

```
## S3 method for class 'stress_design'
plot(x, target = 0.8, ...)
```

Arguments

x A stress_design object from [stress_design\(\)](#).
 target Reference line for the robustness power.
 ... Ignored.

Value

A ggplot: the probability of a significant result and of a significant and robust result against subjects per arm, one panel per effect size.

plot_pcdf

*Empirical distribution of the p-values across a census***Description**

The empirical cumulative distribution of the p-values of every counted refit, against the uniform diagonal that a result with no true effect would produce (the p-value of each refit of a null result is uniform, so the curve of a null census hugs the diagonal; a census far above it is far from random). One curve per census when several are given, with the pooled curve in black; the share below alpha is annotated.

Usage

```
plot_pcdf(x, alpha = NULL, pooled = TRUE)
```

Arguments

x	A stress_census, or a named list of them.
alpha	Significance level; defaults to the census's own.
pooled	Draw the pooled curve over all censuses.

Details

The refits are not independent, so the curve is a description, not a test.

Value

A ggplot object.

Examples

```
small <- mrmr::fev_data[mrmr::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
cen <- stress_census(spec, stress_covariance(spec, c("cs", "ar1h")), stress_loo(spec, by = "RACE"))
if (requireNamespace("ggplot2", quietly = TRUE)) plot_pcdf(cen)
```

plot_pcurve

*Plot p-value curves over a continuous perturbation***Description**

Draws the p-value against the parameter for every family of rows that carries a param value (from `stress_tipping()` or `stress_curve()`): one line per family, the alpha reference line, the anchor point (the row of kind = "alternative", usually the unshifted analysis) emphasised, and a dotted vertical line at each interpolated crossing with its value.

Usage

```
plot_pcurve(
  rows,
  alpha = NULL,
  xlab = "Perturbation",
  ylab = "p-value",
  log_p = FALSE
)
```

Arguments

rows	A stress_rows data frame or stress_census; rows without a param are ignored.
alpha	Significance level; defaults to the rows' own alpha.
xlab, ylab	Axis labels.
log_p	Draw the p-value axis on a log scale.

Value

A ggplot object.

Examples

```
small <- mrmr::fev_data[mrmr::fev_data$USUBJID %in% paste0("PT", 1:80), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL)
tp <- stress_tipping(spec, deltas = c(0, -4, -8), m = 3)
if (requireNamespace("ggplot2", quietly = TRUE)) plot_pcurve(tp)
```

plot_pstrip	<i>Strip plot of p-values after each deletion</i>
-------------	---

Description

Each dot is one refit with one unit removed, on a p-value axis (linear by default, log on request), one strip per leave-one-out family; the diamond is the pre-specified analysis with nothing removed and the dashed line is alpha. Counts of deletions below alpha label each strip.

Usage

```
plot_pstrip(x, alpha = NULL, log_p = FALSE, xmax = NULL, label_family = TRUE)
```

Arguments

x	A stress_census, or a named list of them (one strip each).
alpha	Significance level; defaults to the census's own.
log_p	Draw the p-value axis on a log scale (spreads out the small p-values; harder to read for most audiences).
xmax	Upper limit of the linear p-value axis; NULL fits the data.
label_family	Include the deletion family in each strip label; set FALSE when every census contributes one family (subjects only, say).

Value

A ggplot object.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
cen <- stress_census(spec, stress_loo(spec, by = "RACE"), stress_loo(spec, by = "SEX"))
if (requireNamespace("ggplot2", quietly = TRUE)) plot_pstrip(cen)
```

plot_swarm	<i>Bubble-swarm plot of a census against the no-difference line</i>
------------	---

Description

One row per census. Each bubble is one distinct estimate among the counted alternative analyses (rounded to digits), with area proportional to the number of analyses giving that value and shade by the share of those analyses that are significant; bubbles holding five or more analyses are numbered. A ring marks the pre-specified estimate, the shaded band holds the central 95% of the distinct values, the heavy vertical line is no difference, and the least favourable alternative is labelled. Deletions are a strip of small light dots beneath the swarm.

Usage

```
plot_swarm(
  x,
  scale = c("percent", "estimate"),
  digits = 2,
  r0 = 0.004,
  favours = NULL,
  xlab = NULL,
  xlim = NULL
)
```

Arguments

x	A stress_census, or a named list of them (one row each, drawn on a shared axis; the first is drawn at the top).
scale	"percent" draws estimates as a percent of the pre-specified estimate, so several endpoints share an axis; "estimate" uses the response units (only sensible for one census or censuses on one scale).
digits	Rounding used to decide which estimates are "the same value".
r0	Radius of a count-one bubble as a fraction of the x-axis range.
favours	Labels for the two sides of no difference, in the order (reference arm, active arm). Defaults to the treatment level names.
xlab	Axis label; NULL for a default.
xlim	Axis limits; NULL for automatic limits that include zero.

Value

A ggplot object (uses a fixed aspect ratio so bubbles are round).

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
cen <- stress_census(spec, stress_covariance(spec, c("us", "cs", "ar1h", "toep")),
  stress_covariates(spec), stress_loo(spec, by = "RACE"))
if (requireNamespace("ggplot2", quietly = TRUE)) plot_swarm(cen)
```

run_plan

*Run a pre-specified stress test***Description**

Runs every family in a `stress_plan()`, assembles the census and the verdict, and keeps the rows by family.

Usage

```
run_plan(plan, cores = 1L, seed = 1)
```

Arguments

plan	A stress_plan.
cores	Worker processes; the cluster is started once and shared by every family.
seed	Seed passed to the families that take one, unless the plan sets it.

Value

An object of class `stress_result`: plan, rows (a list of stress_rows by family), census, verdict, base and elapsed.

Examples

```
small <- mrmr::fev_data[mrmr::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
plan <- stress_plan(spec, covariance = list(structures = c("cs", "ar1h")),
  inference = NULL, covariates = NULL, weights = FALSE,
  loo = list(by = "RACE"), permute = list(n = 9), reference = NULL,
  estimator = list(estimators = "ancova"), fragility = list(max_k = 1))
res <- run_plan(plan)
res
```

run_plans

Run several plans (several endpoints or comparisons) and compare

Description

Run several plans (several endpoints or comparisons) and compare

Usage

```
run_plans(plans, cores = 1L, seed = 1)
```

Arguments

plans	A named list of stress_plan objects.
cores, seed	Passed to run_plan() .

Value

A named list of `stress_result` objects of class `stress_results`; `summary()` gives one line per plan and `plot_swarm()` accepts the censuses (`lapply(results, function(r) r$census)`).

Examples

```

small <- mrmr::fev_data[mrmr::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
                    covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
mk <- function(s) stress_plan(s, covariance = list(structures = c("cs", "ar1h")), inference = NULL,
                             covariates = NULL, weights = FALSE, loo = NULL, permute = NULL,
                             reference = NULL, estimator = NULL, fragility = NULL)
res <- run_plans(list(VIS4 = mk(spec), VIS3 = mk(spec_update(spec, contrast_visit = "VIS3"))))
summary(res)

```

simulate_trial

*Simulate a two-arm longitudinal trial***Description**

Multivariate-normal responses at `n_visits` post-baseline visits with an AR(1) correlation, a baseline covariate, a treatment effect growing linearly to `delta` at the last visit, and dropout after each visit whose probability rises as the current value falls (missing at random).

Usage

```

simulate_trial(
  n_per_arm = 50,
  delta = 0,
  n_visits = 4,
  sigma = 10,
  rho = 0.6,
  dropout = 0.08,
  baseline_beta = 0.5,
  errors = c("normal", "t"),
  t_df = 3,
  hetero = 1,
  mnar = 0,
  interaction = 0,
  seed = NULL
)

```

Arguments

<code>n_per_arm</code>	Subjects per arm.
<code>delta</code>	Treatment effect at the last visit (active minus reference).
<code>n_visits</code>	Number of post-baseline visits.
<code>sigma</code>	Residual standard deviation at each visit.
<code>rho</code>	AR(1) correlation between adjacent visits.
<code>dropout</code>	Baseline per-visit dropout probability.

baseline_beta	Slope of the response on the baseline covariate.
errors	"normal" or "t" (Student t with t_df degrees of freedom, scaled to the same standard deviation: heavy tails).
t_df	Degrees of freedom for errors = "t".
hetero	Multiplier of the residual standard deviation at the last visit relative to the first (1 = homoscedastic); the SD grows linearly.
mnar	Strength of missing-not-at-random dropout: dropout after a visit depends on the value the subject would have had at the NEXT visit (0 = missing at random, as the default).
interaction	Treatment effect modification by the baseline covariate: the effect at the last visit is $\text{delta} * (1 + \text{interaction} * (\text{base} - 50) / 10)$.
seed	Random seed.

Value

A long data frame with id, arm ("REF", "ACT"), base, visit ("V1", ...) and y, missing rows removed.

Examples

```
d <- simulate_trial(40, delta = 3, seed = 1); head(d)
```

spec_update

Modify a stress spec

Description

Returns a copy of spec with the named settings replaced. Settings that change the data conventions (reference, visit, treatment, subject, response) cannot be changed here; build a new spec instead.

Usage

```
spec_update(spec, ...)
```

Arguments

spec	A stress_spec.
...	Settings to replace: covariance, method, vcov, covariates, contrast_visit, alpha, label, data, weights, active.

Value

The modified stress_spec.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
spec_update(spec, covariance = "ar1h", method = "Satterthwaite", vcov = "Asymptotic")
```

standard_plan	<i>The standard stress test</i>
---------------	---------------------------------

Description

A recommended, citable set of families with fixed settings, so that a statistical analysis plan can say "the standard stress test of ballast" and mean one thing. It contains, in order:

Usage

```
standard_plan(
  spec,
  site = NULL,
  strata = site,
  baseline = NULL,
  deltas = NULL,
  shift_visits = NULL,
  ice = NULL,
  m = 25,
  n_perm = 2000,
  max_k = 5
)
```

Arguments

spec	A stress_spec() .
site	Optional site or centre column (deletions, random intercept, re-randomisation strata unless strata is given).
strata	Optional stratification column for the re-randomisation test.
baseline	Optional baseline column for cLDA.
deltas	Optional shifts for the tipping-point family.
shift_visits	Visits whose imputed values the tipping family shifts; NULL shifts the contrast visit only (the plan text states the visits; pass every visit level to shift all imputed values).
ice	Optional intercurrent-event table for stress_estimand() .
m	Imputations for the multiple-imputation families.
n_perm	Permutations for the re-randomisation test.
max_k	Maximum removals in the deletion search.

Details

1. covariance structure: us, ar1h, ar1, cs, csh, toep, toepr;
2. inference: Satterthwaite, Kenward-Roger, linear Kenward-Roger, residual, sandwich with between-within df, jackknife sandwich;
3. covariate set: each covariate dropped, all dropped;
4. LS-mean weighting: equal and observed margins;
5. leave-one-out: every subject, and every level of site if given;
6. re-randomisation test: 2,000 permutations, within strata if given;
7. reference-based multiple imputation: MAR, J2R, CR, CIR, 25 imputations;
8. delta-adjusted multiple imputation over deltas if given;
9. estimator class: complete cases, GEE independence, ANCOVA, robust ANCOVA, plus a random intercept for site and cLDA for baseline if given;
10. greedy deletion search for the loss of significance, up to 5 subjects;
11. intercurrent-event strategies if ice is given (treatment policy, hypothetical, while on treatment).

Value

A `stress_plan`.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
standard_plan(spec, site = "RACE", baseline = "FEV1_BL")
```

stress_calibrate	<i>Pre-trial calibration of the stress test</i>
------------------	---

Description

Simulates trials from a planned design and runs a light stress test on each (covariance, inference, covariate, weighting and leave-one-out families, plus the greedy deletion search if `fragility = TRUE`), so that a sponsor can see, before unblinding, how often a trial of this design would be classed robust, sensitive or fragile at each power, and how often the marginal flag would be set.

Usage

```
stress_calibrate(
  n_per_arm = 50,
  power = c(0, 0.5, 0.8, 0.95),
  n_trials = 100,
  n_visits = 4,
  sigma = 10,
```

```

    rho = 0.6,
    dropout = 0.08,
    baseline_beta = 0.5,
    errors = "normal",
    t_df = 3,
    hetero = 1,
    mnar = 0,
    interaction = 0,
    fragility = FALSE,
    cores = 1L,
    seed = 1
  )

```

Arguments

n_per_arm	Subjects per arm.
power	Target powers for the pre-specified analysis; the effect size giving each is derived from the design (0 gives the null).
n_trials	Trials per power.
n_visits	Number of post-baseline visits.
sigma	Residual standard deviation at each visit.
rho	AR(1) correlation between adjacent visits.
dropout	Baseline per-visit dropout probability.
baseline_beta	Slope of the response on the baseline covariate.
errors, t_df, hetero, mnar, interaction	Misspecification settings passed to simulate_trial() .
fragility	Run the deletion search (slower).
cores	Worker processes (the trials are distributed, so each trial's families run on one core).
seed	Base seed.

Value

A data frame of class `stress_calibration` with one row per power: the effect size, observed power, and the proportion of trials with each verdict, the marginal flag, and (if run) a one-subject fragility; `attr(, "trials")` holds the per-trial rows.

Examples

```
stress_calibrate(n_per_arm = 20, power = c(0, 0.8), n_trials = 2)
```

stress_census	<i>Assemble a census of perturbations against the base analysis</i>
---------------	---

Description

Binds the rows returned by the family functions and scores each against the pre-specified (base) fit: percent of the base estimate, shift in base standard errors, whether the estimate lies inside the base confidence interval, keeps the base direction, is significant at alpha, and whether significance changed. Rows that reproduce the base (is_base), did not converge, are tipping-point searches, or duplicate an earlier row are not counted.

Usage

```
stress_census(spec, ..., base = NULL)
```

Arguments

spec	A <code>stress_spec()</code> ; the base fit is <code>stress_fit(spec)</code> .
...	stress_rows data frames from the family functions.
base	Optional pre-computed base row, to avoid refitting.

Value

A data frame of class `stress_census` with the family rows plus `pct_of_base`, `shift_se`, `inside_ci`, `same_direction`, `significant`, `crossed`, `duplicate` (a later row numerically identical to an earlier counted row, so the same specification reached by two families), `counted`; the base row is `attr(, "base")`.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
cen <- stress_census(spec, stress_covariance(spec, c("us", "cs", "ar1h")),
  stress_covariates(spec))
summary(cen)
stress_verdict(cen)
```

stress_covariance	<i>Perturbation family: within-subject covariance structure</i>
-------------------	---

Description

Refits the pre-specified model under each covariance structure. The row that reproduces the spec's own structure is flagged `is_base`.

Usage

```
stress_covariance(
  spec,
  structures = c("us", "ar1h", "ar1", "cs", "csh", "toep", "toeph"),
  cores = 1L
)
```

Arguments

`spec` A [stress_spec\(\)](#).

`structures` Covariance structure names (see [stress_spec\(\)](#)).

`cores` Number of worker processes; 1 fits sequentially.

Value

A `stress_rows` data frame, one row per structure.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_covariance(spec, c("us", "cs", "ar1h"))
```

stress_covariates	<i>Perturbation family: covariate set</i>
-------------------	---

Description

Refits the model with each covariate dropped in turn, with no covariates, and with any user-supplied covariate sets.

Usage

```
stress_covariates(
  spec,
  drop_each = TRUE,
  drop_all = TRUE,
  sets = list(),
  cores = 1L
)
```

Arguments

spec	A <code>stress_spec()</code> .
drop_each	Drop each pre-specified covariate term in turn.
drop_all	Fit with treatment and visit only.
sets	Named list of additional covariate sets (formulas or character vectors of term labels); each is fitted as given.
cores	Number of worker processes; 1 fits sequentially.

Value

A `stress_rows` data frame.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_covariates(spec, sets = list("with weight" = ~ RACE + SEX + FEV1_BL + WEIGHT))
```

stress_curve

Perturbation family: a curve over a continuous data perturbation

Description

Applies a user-supplied modification to the spec's data at each value of a continuous parameter, refits the pre-specified model and returns one row per value with the value in param. This generalises tipping-point searches that are not multiple-imputation based: assigning a contested participant a post-deviation trajectory, shifting one arm's observed values, moving a baseline definition, and so on. Rows are kind = "search" except the row at anchor, which is a counted alternative.

Usage

```
stress_curve(
  spec,
  values,
  modify,
  family = "perturbation curve",
  anchor = NULL,
  role = "sensitivity",
  cores = 1L
)
```

Arguments

spec	A <code>stress_spec()</code> .
values	Numeric vector of parameter values.
modify	A function <code>function(data, value)</code> returning a data frame in the spec's layout. It receives the spec's own data.
family	Family label for the rows.
anchor	The parameter value (if any) that represents an alternative analysis in its own right rather than a search point; NULL for none.
role	"sensitivity" or "supplementary"; see <code>stress_fit()</code> .
cores	Number of worker processes; 1 fits sequentially.

Value

A `stress_rows` data frame, one row per value, with `param` set.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL)
# shift every observed value of one subject on the active arm
shift_pt3 <- function(d, v) { k <- d$USUBJID == "PT3"; d$FEV1[k] <- d$FEV1[k] + v; d }
cv <- stress_curve(spec, values = c(-20, -10, 0, 10, 20), modify = shift_pt3, anchor = 0)
tipping_point(cv)
```

stress_data

Perturbation family: alternative analysis data sets

Description

The generic data-decision family. Each alternative is a data frame in the spec's layout (an intercurrent-event handling, a different baseline definition, a contested record reversed, a different visit window). The pre-specified model is refitted on each.

Usage

```
stress_data(
  spec,
  alternatives,
  family = "data handling",
  role = "supplementary",
  cores = 1L
)
```

Arguments

spec	A <code>stress_spec()</code> .
alternatives	Named list of data frames.
family	Family label for the rows.
role	"supplementary" (the default: an alternative data set usually targets a different estimand) or "sensitivity".
cores	Number of worker processes; 1 fits sequentially.

Value

A `stress_rows` data frame, one row per alternative.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
alt <- mmr::fev_data
alt$FEV1[alt$USUBJID == "PT1"] <- NA # one subject's records set missing
stress_data(spec, list("PT1 removed" = alt))
```

stress_design	<i>Size a trial for a robust result</i>
---------------	---

Description

Simulates trials from a planned design over a grid of sample sizes and effect sizes, runs the light stress test on each (covariance, inference, covariate, weighting and leave-one-subject-out families) and reports, for every cell, the conventional power next to the robustness power: the probability that the pre-specified analysis is significant and classed robust. The deletion search and a delta-adjusted tipping grid are optional and give the expected fragility index and the shift the result can absorb. This is the design-stage use of the stress test: choose the sample size so that a true effect is expected to come out robust rather than only significant, and write the expected verdict rates into the statistical analysis plan before unblinding so that the observed verdict has a pre-registered comparison.

Usage

```
stress_design(
  n_per_arm,
  delta,
  n_trials = 100,
  n_visits = 4,
  sigma = 10,
  rho = 0.6,
  dropout = 0.08,
  baseline_beta = 0.5,
```

```

    covariance = "us",
    method = "Satterthwaite",
    vcov = "Asymptotic",
    alpha = 0.05,
    alternatives = c("us", "ar1h", "cs"),
    loo = TRUE,
    fragility = FALSE,
    max_k = 5,
    tipping = FALSE,
    shifts = seq(0, 2, by = 0.25),
    m = 5,
    errors = "normal",
    t_df = 3,
    hetero = 1,
    mnar = 0,
    interaction = 0,
    cores = 1L,
    seed = 1
)

## S3 method for class 'stress_design'
print(x, target = 0.8, ...)

```

Arguments

n_per_arm	Subjects per arm to evaluate (a vector).
delta	Treatment effects at the last visit to evaluate (a vector); include 0 to see the null.
n_trials	Trials per cell.
n_visits	Number of post-baseline visits.
sigma	Residual standard deviation at each visit.
rho	AR(1) correlation between adjacent visits.
dropout	Baseline per-visit dropout probability.
baseline_beta	Slope of the response on the baseline covariate.
covariance, method, vcov	The pre-specified analysis model, as in stress_spec() .
alpha	Two-sided significance level.
alternatives	Covariance structures offered as alternatives; the pre-specified one is removed from the set.
loo	Run the leave-one-subject-out family.
fragility	Run the greedy deletion search for significance up to max_k removals (slow). Otherwise a one-subject loss of significance is read from the leave-one-out rows.
max_k	Removals allowed in the deletion search.
tipping	Run a delta-adjusted tipping grid (imputed active-arm values shifted down) and record the shift at which p crosses alpha.

shifts	Shifts for the tipping grid as multiples of delta (of sigma when delta is 0).
m	Imputations per shift.
errors	"normal" or "t" (Student t with t_df degrees of freedom, scaled to the same standard deviation: heavy tails).
t_df	Degrees of freedom for errors = "t".
hetero	Multiplier of the residual standard deviation at the last visit relative to the first (1 = homoscedastic); the SD grows linearly.
mнар	Strength of missing-not-at-random dropout: dropout after a visit depends on the value the subject would have had at the NEXT visit (0 = missing at random, as the default).
interaction	Treatment effect modification by the baseline covariate: the effect at the last visit is $\text{delta} * (1 + \text{interaction} * (\text{base} - 50) / 10)$.
cores	Worker processes. Trials are distributed, so each trial's families run on one core.
seed	Base seed; every trial's seed is derived from it.
x	A stress_design object.
target	Robustness power to reach; the print method names the smallest sample size per arm that reaches it for each non-zero effect.
...	Ignored.

Details

The light family set offers the alternative covariance structures, three inference methods, the model without the baseline covariate, observed-margin weighting and, if `loo = TRUE`, every single-subject deletion. Deletions dominate the run time at large sample sizes; `loo = FALSE` gives a fast first pass whose verdicts omit the deletion family.

Value

A data frame of class `stress_design` with one row per cell: `n_per_arm`, `delta`, `trials`, `power` (proportion significant), `robustness_power` (significant and robust), `robust_given_sig`, `sensitive_given_sig`, `fragile_given_sig`, `marginal_given_sig`, `k1_given_sig` (one deletion loses significance), `k_reached_given_sig` and `k_median` (deletion search, if run), `tipping_margin` (median shift that crosses alpha among significant trials, as a multiple of delta or sigma) and `tipping_absorbed` (share of significant trials with no crossing within the grid), and `max_shift_se` (median largest shift in pre-specified standard errors). `attr(, "trials")` holds the per-trial rows and `attr(, "design")` the settings. [plot.stress_design\(\)](#) draws power and robustness power against the sample size.

See Also

[stress_calibrate\(\)](#) for the verdict rates of one design at a set of planned powers; [stress_sap\(\)](#) for the analysis-plan text.

Examples

```
des <- stress_design(n_per_arm = c(40, 80), delta = c(0, 5), n_trials = 4, loo = FALSE)
des
```

stress_estimand	<i>Perturbation family: intercurrent-event strategies (ICH E9(R1))</i>
-----------------	--

Description

Declares the intercurrent events that occurred and derives the analysis data set implied by each handling strategy, then refits the pre-specified model on each. Strategies per event type:

Usage

```
stress_estimand(
  spec,
  ice,
  strategies = c("treatment_policy", "hypothetical", "while_on_treatment", "composite"),
  composite_value = NULL,
  cores = 1L
)
```

Arguments

spec	A stress_spec() .
ice	A data frame with one row per intercurrent event: the subject identifier (column named as the spec's subject), the first visit affected (column named as the spec's visit) and type (a label such as "discontinuation" or "rescue").
strategies	Named list, one element per event type, each a character vector of strategies to apply; or a single character vector applied to every type.
composite_value	A number or function used by the composite strategy.
cores	Number of worker processes; 1 fits sequentially.

Details

- "treatment_policy": use the data as observed, whatever happened.
- "hypothetical": set the responses at and after the event to missing; the model's missing-at-random assumption then supplies the value the subject would have had without the event.
- "while_on_treatment": drop the records at and after the event.
- "composite": replace the responses at and after the event with an unfavourable value: a number, or a function `function(data, rows)` returning one value per affected row (the worst observed change in the subject's arm at that visit, say).

With several event types the strategies are crossed, one row per combination, and the row that applies "treatment_policy" to every type reproduces the pre-specified data and is flagged `is_base`. Every other row targets a different estimand, so they are `role = "supplementary"`; a hypothetical strategy can be followed by [stress_reference\(\)](#) on the derived data for its reference-based sensitivity analyses.

Value

A `stress_rows` data frame, one row per strategy combination; `attr(, "data")` holds the derived data sets by label.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:80), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
ice <- data.frame(USUBJID = c("PT2", "PT5", "PT9"), AVISIT = c("VIS3", "VIS2", "VIS4"),
  type = c("discontinuation", "discontinuation", "rescue"))
strat <- list(discontinuation = c("treatment_policy", "hypothetical"),
  rescue = c("treatment_policy", "composite"))
stress_estimand(spec, ice, strategies = strat, composite_value = 20)
```

stress_estimator

Perturbation family: estimator class

Description

Refits the question with estimators other than the pre-specified MMRM:

Usage

```
stress_estimator(
  spec,
  estimators = c("complete_cases", "gee_independence", "ancova", "robust_ancova",
    "random_intercept", "clda"),
  random = NULL,
  baseline = NULL,
  seed = 1,
  cores = 1L
)
```

Arguments

<code>spec</code>	A <code>stress_spec()</code> .
<code>estimators</code>	Which estimators to run.
<code>random</code>	Name of a grouping column for "random_intercept" (a site or centre variable that is also one of the spec's covariates).
<code>baseline</code>	Name of the baseline column for "clda"; the response must be change from that baseline.
<code>seed</code>	Seed for the robust regression's random initial estimate.
<code>cores</code>	Number of worker processes; 1 fits sequentially.

Details

- "complete_cases": the pre-specified MMRM on subjects observed at every visit (no reliance on missing-at-random within the likelihood).
- "gee_independence": working-independence weighted least squares with a visit-specific residual variance and a cluster-robust (sandwich) variance, between-within degrees of freedom; no within-subject covariance is modelled. Needs nlme.
- "ancova": analysis of covariance at the contrast visit, observed cases, residual degrees of freedom. Covariate terms involving the visit variable are dropped.
- "robust_ancova": MM-type robust regression at the contrast visit (MASS::rlm), normal-theory inference. Needs MASS.
- "cllda": constrained longitudinal data analysis: the raw outcome (baseline plus the response, which must be a change from baseline) is modelled at baseline and every post-baseline visit with one common baseline mean across arms, an unstructured covariance over all visits and the other covariates as fixed effects; the contrast is the difference in the arms' means at the contrast visit. Needs baseline.
- "random_intercept": the pre-specified fixed effects with random as a random intercept instead of a fixed covariate, the spec's covariance structure within subject where nlme has an equivalent (us, ar1h, ar1, cs, csh); normal-theory inference. Needs nlme and random.

Every estimator reports the same least-squares-mean contrast at the contrast visit (class covariates at equal weights, continuous covariates at their means).

Value

A stress_rows data frame, one row per estimator.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_estimator(spec, c("complete_cases", "ancova"))
```

stress_explain

Explain why an alternative analysis moved

Description

For one row of a census (an alternative that crossed alpha, say), attributes the difference between its estimate and the pre-specified estimate to subjects. Each subject's influence is the change in the contrast when that subject is removed, computed under the pre-specified settings and again under the alternative's settings; the difference of the two influences says how much more (or less) that subject drives the result under the alternative. Subjects are ranked by the absolute difference.

Usage

```
stress_explain(spec, row, data = NULL, top = 10, cores = 1L)
```

Arguments

spec	A <code>stress_spec()</code> .
row	One row of a <code>stress_census</code> or <code>stress_rows</code> data frame.
data	The alternative's data set, if it differs from the spec's.
top	Number of subjects to print.
cores	Number of worker processes; 1 fits sequentially.

Details

The alternative's model settings are read from the row (covariance, method, vcov, covariates). For an alternative that used different data, pass that data as `data`.

Value

A data frame of class `stress_explanation` with one row per subject: `subject`, `arm`, `n_visits`, `infl_base`, `infl_alt`, `difference`, sorted by absolute difference; the row explained is `attr(, "row")` and the two full-data estimates are `attr(, "estimates")`.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:30), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
                    covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
cen <- stress_census(spec, stress_covariates(spec))
stress_explain(spec, cen[1, ], top = 5)
```

stress_fit

Fit one MMRM and return one row

Description

Fits the model described by a `stress_spec()` (optionally on alternative data or with alternative settings) and returns the treatment contrast at the contrast visit as a single row in the package's common schema. This is the engine every family function calls.

Usage

```
stress_fit(
  spec,
  data = NULL,
  label = spec$label,
  family = "base",
  kind = "alternative",
  is_base = is.null(data),
  note = "",
  covariates = spec$covariates,
```

```

    covariance = spec$covariance,
    method = spec$method,
    vcov = spec$vcov,
    at = list(),
    role = "sensitivity",
    weights = spec$weights
  )

```

Arguments

spec	A stress_spec.
data	Alternative data set in the same layout as spec\$data; NULL fits the spec's own data.
label, family, kind	Labels for the output row. kind is one of "alternative" (a counted alternative analysis), "deletion" (a leave-one-out refit) or "search" (a point on a tipping-point grid).
is_base	TRUE when the row reproduces the pre-specified analysis exactly; such rows are not counted in a census.
note	Free text carried into the row.
covariates, covariance, method, vcov	Overrides of the spec's settings.
at	Named list of continuous covariates fixed at a value instead of their mean when forming the least-squares means (SAS LSMEANS ... AT).
role	"sensitivity" for an analysis that keeps the estimand and changes an assumption or a modelling choice; "supplementary" for one that targets a different estimand (ICH E9(R1)).
weights	LS-mean weighting, "equal" or "observed"; see stress_spec() .

Value

A one-row data frame of class stress_rows with columns family, label, kind, role, is_base, converged, note, estimate, stderr, df, lcl, ucl, p, n_subj, n_obs, aicc, param (the numeric value of a continuous perturbation, NA otherwise), covariance, method, vcov, covariates, alpha.

Examples

```

spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_fit(spec)

```

stress_fragility

Smallest set of subjects whose removal changes the conclusion

Description

A greedy forward search: at each step every remaining subject is removed in turn from the current data, the pre-specified model is refitted, and the subject whose removal moves the result furthest towards the target is dropped for good. The search stops when the target is reached or after `max_k` steps. The number of steps needed is a continuous-outcome analogue of the fragility index; because the search is greedy it is an upper bound on the true minimum.

Usage

```
stress_fragility(
  spec,
  target = c("significance", "ci", "direction"),
  max_k = 5,
  candidates = NULL,
  cores = 1L
)
```

Arguments

<code>spec</code>	A <code>stress_spec()</code> .
<code>target</code>	What has to change: "significance" (the p-value crosses alpha in either direction, depending on the base result), "ci" (the estimate leaves the base confidence interval) or "direction" (the estimate changes sign).
<code>max_k</code>	Maximum number of subjects to remove.
<code>candidates</code>	Optional character vector of subject identifiers to restrict the search to (one arm, say).
<code>cores</code>	Number of worker processes; 1 fits sequentially.

Value

A `stress_rows` data frame with one row per step (`kind = "search"`, so the rows are not counted in a census, since the search crosses the target by construction; `param =` number removed, `label =` the subjects removed so far). `attr(, "fragility")` is a list with `target`, `k` (the step at which the target was reached, NA if never), `subjects` and `reached`.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
fr <- stress_fragility(spec, max_k = 2)
attr(fr, "fragility")
```

stress_grid

Perturbation family: crossed specification grid

Description

Fits every combination of the supplied covariance structures, inference settings, covariate sets and data sets (a specification curve). The cell that reproduces the spec is flagged is_base.

Usage

```
stress_grid(
  spec,
  covariance = spec$covariance,
  inference = list(base = list(method = spec$method, vcov = spec$vcov)),
  covariates = list(base = spec$covariates),
  data = list(base = NULL),
  cores = 1L
)
```

Arguments

spec	A stress_spec() .
covariance	Character vector of covariance structures.
inference	Named list of <code>list(method = , vcov =)</code> pairs.
covariates	Named list of covariate sets (formulas or term labels).
data	Named list of data frames; a NULL element is the spec's data.
cores	Number of worker processes; 1 fits sequentially.

Value

A stress_rows data frame, one row per cell, labelled "covariance | inference | covariates | data".

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_grid(spec, covariance = c("us", "cs"),
  covariates = list(full = ~ RACE + SEX + FEV1_BL, baseline = ~ FEV1_BL))
```

stress_html	<i>Interactive HTML report</i>
-------------	--------------------------------

Description

Writes an HTML page (its JavaScript dependencies in a lib folder beside it) with the verdict, the summary table and two interactive figures built with plotly: the bubble swarm, where hovering a bubble lists the specifications that give that estimate, and the deletion strip, where hovering a dot names the subject removed and shows the refit's estimate and p-value. Needs plotly and htmlwidgets.

Usage

```
stress_html(result, file, digits = 2, mask_ids = TRUE)
```

Arguments

result	A stress_result from <code>run_plan()</code> .
file	Path of the HTML file to write. There is no default, so nothing is written unless a path is given.
digits	Rounding used to group estimates into bubbles.
mask_ids	Replace subject identifiers with sequence numbers (on by default: the page is the deliverable most likely to leave the organisation).

Value

The file path, invisibly.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
plan <- stress_plan(spec, covariance = list(structures = c("cs", "ar1h")), inference = NULL,
  covariates = NULL, weights = FALSE, loo = list(by = "RACE"), permute = NULL,
  reference = NULL, estimator = NULL, fragility = NULL)
if (requireNamespace("plotly", quietly = TRUE) && requireNamespace("htmlwidgets", quietly = TRUE))
  stress_html(run_plan(plan), file.path(tempdir(), "stress.html"))
```

stress_inference	<i>Perturbation family: degrees-of-freedom method and variance estimator</i>
------------------	--

Description

Perturbation family: degrees-of-freedom method and variance estimator

Usage

```
stress_inference(spec, settings = default_inference(), cores = 1L)
```

Arguments

spec	A stress_spec() .
settings	Named list of <code>list(method = , vcov =)</code> pairs; see default_inference() .
cores	Number of worker processes; 1 fits sequentially.

Value

A `stress_rows` data frame, one row per setting.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_inference(spec, default_inference()[c("Satterthwaite", "Kenward-Roger (linear)"])]
```

stress_log	<i>Write the run log for an audit trail</i>
------------	---

Description

Records the plan text and its MD5 hash, the seed, the package and R versions, the platform, the elapsed time and the verdict, as JSON if `jsonlite` is installed and as plain text otherwise. The hash of the plan text lets a reviewer confirm that the stress test run is the one that was pre-specified.

Usage

```
stress_log(result, file = NULL, seed = 1)
```

Arguments

result	A <code>stress_result</code> .
file	Path to write; <code>NULL</code> returns the log without writing.
seed	The seed that was passed to run_plan() .

Value

The log as a list, invisibly.

Examples

```
small <- mrmr::fev_data[mrmr::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
plan <- stress_plan(spec, covariance = list(structures = c("cs", "ar1h")), inference = NULL,
  covariates = NULL, weights = FALSE, loo = NULL, permute = NULL,
  reference = NULL, estimator = NULL, fragility = NULL)
str(stress_log(run_plan(plan)))
```

stress_loo

Perturbation family: leave-one-out deletions

Description

Refits the model with each subject removed, or with each level of a grouping variable (site, cohort, country) removed. Rows are kind = "deletion" and are summarised separately from alternative analyses.

Usage

```
stress_loo(spec, by = NULL, cores = 1L)
```

Arguments

spec	A stress_spec() .
by	Name of a grouping column; NULL deletes subjects one at a time.
cores	Number of worker processes; 1 fits sequentially.

Value

A stress_rows data frame, one row per deleted unit.

Examples

```
small <- mrmr::fev_data[mrmr::fev_data$USUBJID %in% paste0("PT", 1:40), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL)
stress_loo(spec, by = "RACE")
```

stress_permute	<i>Perturbation family: re-randomisation (permutation) test</i>
----------------	---

Description

Permutes treatment labels across subjects, optionally within strata, refits the pre-specified model each time and returns the permutation p-value for the observed contrast. The returned row carries the observed estimate and the permutation p; the null distribution is attached as `attr(, "null")`.

Usage

```
stress_permute(
  spec,
  n = 1000,
  strata = NULL,
  statistic = c("estimate", "t"),
  seed = 1,
  cores = 1L
)
```

Arguments

spec	A <code>stress_spec()</code> .
n	Number of permutations.
strata	Name of a subject-level column to permute within; NULL permutes freely.
statistic	"estimate" (the contrast; the permutation refits skip the adjusted degrees of freedom, so this is the fast choice) or "t" (estimate over its standard error, refitted with the spec's inference).
seed	Random seed.
cores	Number of worker processes; 1 fits sequentially.

Value

A one-row `stress_rows` data frame with `p` equal to $(1 + \text{number of } |null| \geq |observed|) / (n + 1)$.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL)
stress_permute(spec, n = 19)
```

stress_plan	<i>Pre-specify a stress test</i>
-------------	----------------------------------

Description

A plan names the families to run and their settings before unblinding, so the stress test can be written into a statistical analysis plan and run with one call (`run_plan()`). Each family argument is `NULL` to skip the family, an empty `list()` to run it with its defaults, or a named list of arguments for the family function. Printing the plan gives the text a statistical analysis plan can carry.

Usage

```
stress_plan(
  spec,
  covariance = list(),
  inference = list(),
  covariates = list(),
  weights = TRUE,
  population = NULL,
  data = NULL,
  loo = list(),
  grid = NULL,
  permute = list(n = 2000),
  tipping = NULL,
  reference = list(),
  estimator = list(),
  fragility = list(),
  curve = NULL,
  estimand = NULL,
  visits = NULL,
  title = "Pre-specified stress test"
)
```

Arguments

spec	A <code>stress_spec()</code> : the pre-specified analysis.
covariance	Arguments for <code>stress_covariance()</code> .
inference	Arguments for <code>stress_inference()</code> .
covariates	Arguments for <code>stress_covariates()</code> .
weights	TRUE to run <code>stress_weights()</code> .
population	Arguments for <code>stress_population()</code> (needs rules).
data	Arguments for <code>stress_data()</code> (needs alternatives).
loo	Arguments for <code>stress_loo()</code> ; a list of lists runs it several times (subjects and a site variable, say).
grid	Arguments for <code>stress_grid()</code> .

permute	Arguments for <code>stress_permute()</code> .
tipping	Arguments for <code>stress_tipping()</code> (needs deltas).
reference	Arguments for <code>stress_reference()</code> .
estimator	Arguments for <code>stress_estimator()</code> .
fragility	Arguments for <code>stress_fragility()</code> .
curve	Arguments for <code>stress_curve()</code> (needs values and modify).
estimand	Arguments for <code>stress_estimand()</code> (needs ice).
visits	Arguments for <code>stress_visits()</code> .
title	A title for the plan.

Value

An object of class `stress_plan`.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
plan <- stress_plan(spec, covariance = list(structures = c("us", "cs", "ar1h")),
  inference = list(), covariates = list(), loo = list(by = "RACE"),
  permute = NULL, reference = NULL, estimator = list(estimators = "ancova"),
  fragility = list(max_k = 2))
plan
```

stress_population	<i>Perturbation family: analysis population</i>
-------------------	---

Description

Each rule is a function of the spec's data returning a logical vector of rows to keep (a per-protocol flag, a completer definition, a cohort).

Usage

```
stress_population(spec, rules, role = "supplementary", cores = 1L)
```

Arguments

spec	A <code>stress_spec()</code> .
rules	Named list of functions <code>function(data) logical</code> .
role	"supplementary" (the default: a different population is a different estimand) or "sensitivity".
cores	Number of worker processes; 1 fits sequentially.

Value

A stress_rows data frame, one row per rule.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_population(spec, list("female" = function(d) d$SEX == "Female"))
```

stress_ranktest	<i>Perturbation family: rank tests at the contrast visit</i>
-----------------	--

Description

Model-free tests of the treatment difference in the response at the contrast visit: the Wilcoxon rank-sum test (normal approximation with the tie correction and continuity correction, as SAS PROC NPAR1WAY reports it) and, if strata is given, the van Elteren test (the Cochran-Mantel- Haenszel row-mean-score statistic on modified ridit scores within strata). The rows carry a p-value and the Hodges-Lehmann shift as the estimate, with no standard error or interval; they count towards significance only.

Usage

```
stress_ranktest(spec, strata = NULL, cores = 1L)
```

Arguments

- spec A [stress_spec\(\)](#).
- strata Name of a subject-level stratification column for the van Elteren test; NULL runs the Wilcoxon test only.
- cores Number of worker processes; 1 fits sequentially.

Value

A stress_rows data frame with one or two rows.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_ranktest(spec, strata = "RACE")
```

stress_reference	<i>Perturbation family: reference-based multiple imputation</i>
------------------	---

Description

Imputes the missing responses from a multivariate-normal imputation model (an MMRM on the observed data with treatment by visit, the subject-level covariates and an unstructured covariance) under the standard reference-based assumptions (Carpenter, Roger and Kenward, 2013), refits the pre-specified model on each completed data set and pools with Rubin's rules:

Usage

```
stress_reference(
  spec,
  methods = c("MAR", "J2R", "CR", "CIR"),
  m = 25,
  seed = 1,
  delta = 0,
  arm = NULL,
  impute_covariates = NULL,
  same_cov = TRUE,
  max_tries = 3L,
  cores = 1L
)
```

Arguments

spec	A stress_spec() .
methods	Assumptions to run, from "MAR", "J2R", "CR", "CIR".
m	Number of imputations.
seed	Random seed (the same seed is used for every delta).
delta	Shift added to the active arm's imputed values (response units); 0 for none.
arm	Treatment level receiving the shift; defaults to the active arm.
impute_covariates	Subject-level covariates used as predictors in the imputation model (with treatment and the visit columns); NULL uses every spec covariate that is constant within subject. Covariates that vary within subject cannot be used.
same_cov	If TRUE one covariance matrix is shared by both arms in the imputation model; if FALSE each arm has its own, and the reference arm's is used for the reference-based draws.
max_tries	Bootstrap refits attempted per imputation before giving up.
cores	Number of worker processes; 1 fits sequentially.

Details

- MAR: every subject's missing values follow their own arm.
- J2R (jump to reference): an active-arm subject's visits after the last observed one take the reference arm's means.
- CR (copy reference): an active-arm subject with any missing value follows the reference arm's means at every visit.
- CIR (copy increments in reference): after the last observed visit the subject keeps their own-arm mean at that visit and then changes as the reference arm does.

Visits missing before the last observed one are treated as missing at random under every assumption. Parameter uncertainty is carried by approximate Bayesian draws: for each imputation the imputation model is refitted on a bootstrap sample of subjects (stratified by arm) and its fixed effects and covariance are used to draw the missing values from the conditional normal distribution given the subject's observed values. An optional `delta` is added to every imputed value of the active arm.

Imputation `i` uses seed `seed + i` on whichever worker draws it, so the result is the same for any number of cores.

Value

A `stress_rows` data frame, one counted row per method (`role = "sensitivity"`), with the number of imputations and the Monte Carlo standard error in `note`.

References

Carpenter JR, Roger JH, Kenward MG (2013). Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. *Journal of Biopharmaceutical Statistics* 23, 1352-1371.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:100), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
stress_reference(spec, methods = c("MAR", "J2R"), m = 3)
```

stress_report

Write a stress-test report

Description

Writes a Markdown report with the plan, the base analysis, the per-family summary table, the verdict and the standard figures (census dot plot, bubble swarm, deletion p-value strip, p-value curves where the result has rows with a parameter) as PNG files beside it.

Usage

```
stress_report(
  result,
  dir,
  name = "stress_report",
  width = 9,
  height = 5,
  dpi = 150,
  mask_ids = FALSE
)
```

Arguments

result	A stress_result from <code>run_plan()</code> .
dir	Directory to write into (created if needed). There is no default, so nothing is written unless a location is given.
name	File stem for the report and figures.
width, height, dpi	Figure size in inches and resolution.
mask_ids	Replace subject identifiers with sequence numbers.

Value

The path of the Markdown file, invisibly.

Examples

```
small <- mrm::fev_data[mrm::fev_data$USUBJID %in% paste0("PT", 1:60), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")
plan <- stress_plan(spec, covariance = list(structures = c("cs", "ar1h")), inference = NULL,
  covariates = NULL, weights = FALSE, loo = list(by = "RACE"), permute = NULL,
  reference = NULL, estimator = NULL, fragility = NULL)
stress_report(run_plan(plan), dir = tempdir())
```

stress_sap

Statistical-analysis-plan text for a stress test

Description

Returns the paragraphs a statistical analysis plan can carry to pre-specify a stress test: the purpose, the pre-specified analysis, the families and their settings (from the plan), the counting rule, the classification, what will be reported, and the plan's MD5 hash so the run after unblinding can be shown to match what was pre-specified. The same text is installed as a template at `system.file("templates", "sap_stress_test.md", package = "ballast")`.

Usage

```
stress_sap(plan, file = NULL, trial = "the study")
```

Arguments

plan	A stress_plan() .
file	Optional path to write the text to (Markdown).
trial	A short name for the trial, used in the text.

Value

A character vector of paragraphs, invisibly if file is given.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
cat(stress_sap(standard_plan(spec, site = "RACE"), trial = "Study 001"), sep = "\n\n")
```

stress_spec

Define the pre-specified MMRM to stress-test

Description

A `stress_spec` holds the analysis data and every decision of the pre-specified mixed model for repeated measures: the response, subject, visit and treatment variables, the covariates, the visit at which the treatment contrast is taken, the within-subject covariance structure, the degrees-of-freedom method, the variance estimator and the significance level. Every family function in the package takes a spec and returns rows in the schema of [stress_fit\(\)](#).

Usage

```
stress_spec(
  data,
  response,
  subject,
  visit,
  treatment,
  reference = NULL,
  active = NULL,
  covariates = NULL,
  contrast_visit = NULL,
  covariance = "us",
  method = "Kenward-Roger",
  vcov = "Kenward-Roger-Linear",
  alpha = 0.05,
  weights = c("equal", "observed"),
```

```

    label = "pre-specified",
    sas_conventions = TRUE,
    time = NULL
  )

```

Arguments

<code>data</code>	A data frame in long format, one row per subject and visit.
<code>response</code>	Name of the response column (change from baseline, say).
<code>subject</code>	Name of the subject identifier column.
<code>visit</code>	Name of the visit column; coerced to a factor whose level order is the visit order.
<code>treatment</code>	Name of the treatment column (two or more arms).
<code>reference</code>	The reference (control) level of treatment. Defaults to the first factor level.
<code>active</code>	The treatment level compared with the reference. Defaults to the first non-reference level. With three or more arms, change it with <code>spec_update()</code> to stress-test each comparison in turn.
<code>covariates</code>	Fixed-effect covariates besides treatment and visit, as a one-sided formula ($\sim$ base + site) or a character vector of term labels. Character and logical columns are treated as class variables.
<code>contrast_visit</code>	The visit level at which the treatment contrast is estimated. Defaults to the last visit level.
<code>covariance</code>	Covariance structure name as used by <code>mmrm</code> : "us", "ar1", "ar1h", "cs", "csh", "toep", "toeph", "ad", "adh", or "sp_exp" (spatial exponential, the SAS SP(POW) structure, on the continuous time variable).
<code>method</code>	Degrees-of-freedom method passed to <code>mmrm::mmrm_control()</code> : "Satterthwaite", "Kenward-Roger", "Residual" or "Between-Within".
<code>vcov</code>	Variance estimator passed to <code>mmrm::mmrm_control()</code> : "Asymptotic", "Empirical", "Empirical-Jackknife", "Empirical-Bias-Reduced", "Kenward-Roger" or "Kenward-Roger-Linear". The SAS DDFM=KR default corresponds to method = "Kenward-Roger" with <code>vcov</code> = "Kenward-Roger-Linear".
<code>alpha</code>	Two-sided significance level.
<code>weights</code>	How class covariates are weighted in the least-squares means: "equal" (every level equally, SAS LSMEANS default) or "observed" (the design is averaged over the covariate values of the analysis rows, as SAS OBSMARGINS and g-computation do).
<code>label</code>	Label for the base analysis in output rows.
<code>sas_conventions</code>	If TRUE, the between-within degrees of freedom for a sandwich-variance contrast are computed as SAS PROC MIXED does when EMPIRICAL is combined with a DDFM it cannot honour (observations minus subjects minus the rank of the within-subject design columns).
<code>time</code>	Name of a numeric time column for the "sp_exp" structure (days from randomisation, say; <code>mmrm</code> converges more readily with time rescaled to hundreds of days).

Details

The fixed effects are `covariates + treatment + visit + treatment:visit`; the treatment contrast at `contrast_visit` is the difference of least-squares means (active minus reference) with class covariates weighted equally over their levels and continuous covariates at their means, the convention of SAS LSMEANS.

Value

An object of class `stress_spec`.

Examples

```
spec <- stress_spec(mmr::fev_data, response = "FEV1", subject = "USUBJID",
  visit = "AVISIT", treatment = "ARMCD", reference = "PBO",
  covariates = ~ RACE + SEX + FEV1_BL, contrast_visit = "VIS4")
spec
```

<code>stress_spec_adam</code>	<i>Build a stress spec from an ADaM basic data structure</i>
-------------------------------	--

Description

Subsets a CDISC ADaM BDS data set (ADEFF, ADQS and the like) to one parameter, the analysis-flagged post-baseline records, orders the visits by their numeric code and builds the spec with the baseline value as a covariate by default.

Usage

```
stress_spec_adam(
  bds,
  paramcd,
  response = "CHG",
  subject = "USUBJID",
  visit = "AVISIT",
  visitn = "AVISITN",
  treatment = "TRTP",
  reference = NULL,
  active = NULL,
  covariates = ~BASE,
  contrast_visit = NULL,
  analysis_flag = "ANL01FL",
  drop_baseline = TRUE,
  filter = NULL,
  covariance = "us",
  method = "Kenward-Roger",
  vcov = "Kenward-Roger-Linear",
  alpha = 0.05,
```

```
  weights = "equal",
  label = paste(paramcd, response)
)
```

Arguments

- bds A BDS data frame.
- paramcd The PARAMCD value to analyse.
- response Response column, usually "CHG" or "PCHG".
- subject, visit, visitn, treatment
 Column names (USUBJID, AVISIT, AVISITN, TRTP by default).
- reference, active, contrast_visit, covariance, method, vcov, alpha, weights, label
 As in [stress_spec\(\)](#).
- covariates Covariates; the default is the baseline value BASE.
- analysis_flag Name of a flag column kept where equal to "Y"; NULL keeps all records.
- drop_baseline Drop records flagged ABLFL == "Y" or with a non-positive visitn.
- filter Optional function of the data returning the rows to keep, applied after the other subsets (an analysis-phase restriction, say).

Value

A stress_spec.

Examples

```
bds <- transform(mmrn::fev_data, PARAMCD = "FEV1", CHG = FEV1 - FEV1_BL, BASE = FEV1_BL,
  AVISITN = VISITN, TRTP = ARMCD, ANL01FL = "Y")
stress_spec_adam(bds, "FEV1", response = "CHG", visit = "AVISIT", reference = "PB0")
```

stress_spec_mmrn	<i>Build a stress spec from a fitted mmrm model</i>
------------------	---

Description

Takes the data, response, subject, visit, covariance structure, degrees-of-freedom method and variance estimator from an mmrm fit. The treatment variable is the factor that interacts with the visit variable unless given.

Usage

```
stress_spec_mmrn(  
  fit,  
  treatment = NULL,  
  reference = NULL,  
  active = NULL,  
  contrast_visit = NULL,  
  alpha = 0.05,  
  weights = "equal",  
  label = "pre-specified",  
  sas_conventions = TRUE  
)
```

Arguments

- fit An object of class mmrm.
- treatment Name of the treatment column; NULL finds the factor in an interaction with the visit variable.
- reference, active, contrast_visit, alpha, weights, label, sas_conventions As in [stress_spec\(\)](#).

Value

A stress_spec.

Examples

```
fit <- mmrm::mmrm(FEV1 ~ RACE + SEX + FEV1_BL + ARMCD * AVISIT + us(AVISIT | USUBJID),  
  data = mmrm::fev_data)  
stress_spec_mmrn(fit, reference = "PBO")
```

stress_tables	Write regulatory-style tables and the census
---------------	--

Description

Writes the per-family summary, the rows that crossed alpha or left the interval, the deletion-search path and the full census. CSV files are always written; with `flextable` and `officer` installed, a Word document with the tables in a standard clinical-report layout is written too, and an RTF version of each table.

Usage

```
stress_tables(  
  result,  
  dir,  
  name = "stress",  
  formats = c("csv", "docx", "rtf"),  
  digits = 3,  
  mask_ids = FALSE  
)
```

Arguments

- result A stress_result from [run_plan\(\)](#).
- dir Directory to write into (created if needed). There is no default, so nothing is written unless a location is given.
- name File stem.
- formats Any of "csv", "docx", "rtf".
- digits Decimal places in the formatted tables.
- mask_ids Replace subject identifiers with sequence numbers.

Value

The paths written, invisibly.

Examples

```
small <- mmrm::fev_data[mmrm::fev_data$USUBJID %in% paste0("PT", 1:60), ]  
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL,  
  covariance = "cs", method = "Satterthwaite", vcov = "Asymptotic")  
plan <- stress_plan(spec, covariance = list(structures = c("cs", "ar1h")), inference = NULL,  
  covariates = NULL, weights = FALSE, loo = list(by = "RACE"), permute = NULL,  
  reference = NULL, estimator = NULL, fragility = NULL)  
stress_tables(run_plan(plan), dir = tempdir(), formats = "csv")
```

stress_tipping	<i>Perturbation family: delta-adjusted multiple imputation (tipping point)</i>
----------------	--

Description

Imputes the missing responses by fully conditional specification (regression method, one column per visit, subject-level covariates and treatment as predictors), adds delta to every imputed value of the active arm, refits the pre-specified model on each completed data set and pools with Rubin's rules. delta = 0 is the missing-at-random multiple-imputation analysis and is a counted alternative; other deltas are tipping-point searches (kind = "search"). Rows carry the delta in param.

Usage

```
stress_tipping(
  spec,
  deltas = seq(0, -10, by = -2),
  m = 25,
  seed = 1,
  arm = NULL,
  shift_visits = NULL,
  impute_covariates = NULL,
  nbiter = 10,
  shift_every = TRUE,
  cores = 1L
)
```

Arguments

spec	A stress_spec() .
deltas	Shifts added to the imputed values of the active arm, in response units.
m	Number of imputations.
seed	Random seed (the same seed is used for every delta).
arm	Treatment level receiving the shift; defaults to the active arm.
shift_visits	Visit levels whose imputed values are shifted; NULL shifts every visit.
impute_covariates	Subject-level covariates used as predictors in the imputation model (with treatment and the visit columns); NULL uses every spec covariate that is constant within subject. Covariates that vary within subject cannot be used.
nbiter	Burn-in iterations of the FCS sampler.
shift_every	If TRUE the shift is applied at every draw (SAS MNAR ADJUST under FCS); if FALSE only to the final imputation.
cores	Number of worker processes; 1 fits sequentially.

Details

Covariates that vary within subject are excluded from the imputation model and are kept in the analysis model; subject-visit rows absent from the data are created for the imputed response with those covariates missing, so they drop out of the refit.

Value

A stress_rows data frame, one row per delta; note records the number of imputations and the Monte Carlo standard error of the pooled estimate.

Examples

```
small <- mrmr::fev_data[mrmr::fev_data$USUBJID %in% paste0("PT", 1:80), ]
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL)
stress_tipping(spec, deltas = c(0, -5), m = 3)
```

stress_verdict	<i>Classify the census: robust, sensitive or fragile, and marginal</i>
----------------	--

Description

Applies the definitions: *fragile* if any counted row reverses the base direction or lies outside the base confidence interval; otherwise *sensitive* if any counted row changes significance at alpha; otherwise *robust*. *Marginal* is a separate flag on the base p-value, true when it lies within $\alpha * \text{marginal_band}$.

Usage

```
stress_verdict(census, marginal_band = c(0.5, 2))
```

Arguments

census	A stress_census.
marginal_band	Multiplicative band around alpha for the marginal flag; the default flags a base p between $\alpha / 2$ and $2 * \alpha$.

Value

A list of class stress_verdict: stability over every counted row, stability_sensitivity over the rows that keep the estimand (role = "sensitivity"), marginal, the counts behind them, and the rows that drove the classification.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
cen <- stress_census(spec, stress_covariance(spec, c("us", "cs")), stress_covariates(spec))
v <- stress_verdict(cen)
v$stability
v
```

stress_visits	<i>Perturbation family: the contrast at every visit</i>
---------------	---

Description

Fits the pre-specified model once per visit and reports the treatment contrast at each; the contrast at the pre-specified visit is flagged is_base. A different visit is a different estimand, so the rows are role = "supplementary".

Usage

```
stress_visits(spec, visits = NULL, cores = 1L)
```

Arguments

spec A `stress_spec()`.
 visits Visit levels; NULL for all.
 cores Number of worker processes; 1 fits sequentially.

Value

A `stress_rows` data frame, one row per visit.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_visits(spec)
```

stress_weights	<i>Perturbation family: least-squares-mean weighting</i>
----------------	--

Description

Refits the pre-specified model and forms the treatment contrast with the other weighting of the class covariates: equal weights over levels (SAS LSMEANS default) versus the observed covariate distribution of the analysis rows (SAS OBSMARGINS, g-computation). The point estimate differs only when a class covariate interacts with treatment or visit; the two rows otherwise coincide.

Usage

```
stress_weights(spec, cores = 1L)
```

Arguments

spec A `stress_spec()`.
 cores Number of worker processes; 1 fits sequentially.

Value

A `stress_rows` data frame with two rows, one flagged `is_base`.

Examples

```
spec <- stress_spec(mmr::fev_data, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO",
  covariates = ~ RACE + SEX + FEV1_BL)
stress_weights(spec)
```

summary.stress_census *Summarise a census by family*

Description

Summarise a census by family

Usage

```
## S3 method for class 'stress_census'
summary(object, ...)
```

Arguments

object	A stress_census.
...	Unused.

Value

A data frame with one row per family, kind and role: counted analyses, number significant, number that crossed alpha, number outside the base confidence interval, number reversing direction, the range of percent of base, and the largest shift in base standard errors. Closing rows total the sensitivity analyses (same estimand) and all counted rows.

tipping_point *Find where a p-value curve crosses alpha*

Description

For rows that carry a param value (from [stress_tipping\(\)](#) or [stress_curve\(\)](#)), interpolates linearly between adjacent parameter values to find where the p-value crosses alpha, separately for each family.

Usage

```
tipping_point(rows, alpha = NULL)
```

Arguments

rows	A stress_rows data frame or a stress_census.
alpha	Significance level; defaults to the rows' own alpha.

Value

A data frame with one row per family: family, n points, param_min, param_max, p_min, p_max, crossing (the interpolated parameter value, NA when the curve does not cross) and direction ("up" when p rises through alpha with increasing parameter, "down" otherwise).

Examples

```
small <- mrmr::fev_data[mrmr::fev_data$USUBJID %in% paste0("PT", 1:60), ]  
spec <- stress_spec(small, "FEV1", "USUBJID", "AVISIT", "ARMCD", "PBO", covariates = ~ FEV1_BL)  
shift_pt3 <- function(d, v) { k <- d$USUBJID == "PT3"; d$FEV1[k] <- d$FEV1[k] + v; d }  
tipping_point(stress_curve(spec, values = c(-20, 0, 20), modify = shift_pt3))
```

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