Package 'tipse'

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Title Tipping Point Analysis for Survival Endpoints

Version 1.1

Description Implements tipping point sensitivity analysis for time-to-event endpoints under different missing data scenarios, as described in Oodally et al. (2025) <doi:10.48550/arXiv.2506.19988>. Supports both model-based and model-free imputation, multiple imputation workflows, plausibility assessment and visualizations. Enables robust assessment for regulatory and exploratory analyses.

License GPL (>= 3)

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LazyData true

Imports MASS, ggplot2, survival, dplyr, stats, utils, knitr, purrr, rmarkdown

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Contents

`assess_plausibility` *Assess Clinical Plausibility of Imputation Results*

Description

This function facilitate the evaluation of clinical plausibility at the tipping point. It provides a text summary comparing event rates, follow-up duration, or hazard ratios between treatment arms depending on the imputation method and arm specified.

Usage

```
assess_plausibility(tipse, verbose = TRUE)
```

Arguments

`tipse`	A `tipse` object returned by one of tipping_point_model_free or tipping_point_model_based.
`verbose`	Logical. If `TRUE`, prints assessment details.

Value

A character string summarizing the key information to facilitate clinical plausibility assessment based on the imputation scenario.

Examples

```
cox1 <- survival::coxph(Surv(AVAL, EVENT) ~ TRT01P, data = codebreak200)
result <- tipping_point_model_free(
  dat = codebreak200,
  reason = "Early dropout",
  impute = "docetaxel",
  cox_fit = cox1,
  method = "random sampling"
)

assess_plausibility(result)
```

codebreak200 *Patient level data from dummy trial*

Description

Based on re-constructed Kaplan-Meier plot from CodeBreak 200 trial (de Langen et al., 2023)

Usage

```
codebreak200
```

Format

A data frame with 345 rows and 5 columns:

SUBJID Dummy patient ID

TRT01P Treatment arm (Sotorasib or Docetaxel)

AVAL PFS time in days

EVENT Indicator for PFS event

CNSRRS Censoring reason (Early dropout or Other)

MAXAVAL Maximum potential survival time, duration between randomization to data cut-off

Source

De Langen, A.J., Johnson, M.L., Mazieres, J., Dingemans, A.M.C., Mountzios, G., Pless, M., Wolf, J., Schuler, M., Lena, H., Skoulidis, F. and Yoneshima, Y., 2023. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial. The Lancet, 401(10378), pp.733-746.

extenet *Patient level data from dummy trial*

Description

Based on re-constructed Kaplan-Meier plot from ExteNET trial (Martin et al., 2017)

Usage

```
extenet
```

Format

A data frame with 2840 rows and 5 columns:

SUBJID Dummy patient ID

TRT01P Treatment arm (Neratinib or placebo)

AVAL iDFS time in days

EVENT Indicator for iDFS event

CNSRRS Censoring reason (Lost to follow-up or Other)

MAXAVAL Maximum potential survival time, duration between randomization to data cut-off

Source

Martin, M., Holmes, F.A., Ejlertsen, B., Delaloge, S., Moy, B., Iwata, H., von Minckwitz, G., Chia, S.K., Mansi, J., Barrios, C.H. and Gnant, M., 2017. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. The lancet oncology, 18(12), pp.1688-1700.

`plot.tipse` *Plot Pooled Kaplan–Meier Curves from Model-Free Tipping Point Analysis*

Description

Visualizes averaged (pooled) Kaplan-Meier survival curves across multiple tipping point parameters, highlighting the tipping point where the upper CL of the hazard ratio crosses 1.

Usage

```
## S3 method for class 'tipse'
plot(x, type = c("Kaplan-Meier", "Tipping Point"), ...)
```

Arguments

`x`	An S3 object of class `"tipse"` returned from tipping_point_model_free or tipping_point_model_based.
`type`	Type of plot, either "Kaplan-Meier" or "Tipping Point".
`...`	Additional arguments not used.

Details

- If `type = Kaplan-Meier`, then the KM curves from multiply imputed datasets were pooled using Rubin's rules after complementary log-log transformation as described in Marshall et al. (2009). it can be of interest to visually assess the scenario that tips the result and the shift it causes to the original KM curve, although there is no objective measure to assess the robustness of the result.
- If `type = Tipping Point`, then the HR estimation across the range of tipping point parameters are plotted.

Value

A ggplot2 object displaying pooled Kaplan–Meier curves.

References

Marshall, A., Altman, D.G., Holder, R.L. et al. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 9, 57 (2009). https://doi.org/10.1186/1471-2288-9-57

Examples

```
cox1 <- survival::coxph(Surv(AVAL, EVENT) ~ TRT01P, data = codebreak200)
result <- tipping_point_model_based(
  dat = codebreak200,
  reason = "Early dropout",
  impute = "docetaxel",
  imputation_model = "weibull",
  J = 10,
  tipping_range = seq(0.1, 1, by = 0.05),
  cox_fit = cox1,
  verbose = TRUE,
  seed = 12345
)
plot(result, type = "Kaplan-Meier")
plot(result, type = "Tipping Point")
```

`summary.tipse` *Summarize Tipping Point Results (ARD Format)*

Description

Creates a concise, analysis-results dataset (ARD) from a tipping point analysis. Identifies the tipping point parameter where the upper CL of the hazard ratio crosses 1 and summarizes key metrics.

Usage

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

Arguments

`object`	A `tipse` object returned by tipping_point_model_free or tipping_point_model_based.
`...`	Additional arguments not used.

Value

A data frame summarizing:

- HR - hazard ratio at that tipping point
- CONFINT - 95% CI at tipping point
- METHOD - sampling type used
- ARMIMP - arm imputed
- TIPPT - parameter where upper CL first crosses 1
- TIPUNIT - parameter meaning
- DESC - textual interpretation

Examples

```
cox1 <- survival::coxph(Surv(AVAL, EVENT) ~ TRT01P, data = codebreak200)
result <- tipping_point_model_based(
  dat = codebreak200,
  reason = "Early dropout",
  impute = "docetaxel",
  imputation_model = "weibull",
  J = 10,
  tipping_range = seq(0.1, 1, by = 0.05),
  cox_fit = cox1,
  verbose = TRUE,
  seed = 12345
)
summary(result)
```

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tipping_point_model_based

Tipping Point Analysis (Model-Based)

Description

Performs a model-based tipping point analysis on time-to-event data by repeatedly imputing censored observations under varying assumptions. The model-based framework assumes that censored patients have a multiple of hazard fitted via a parametric survival model compared to the rest of patients in the same arm (Akinson et al, 2019).

Usage

```
tipping_point_model_based(
  dat,
  reason,
  impute,
  imputation_model = "weibull",
  J = 10,
```

```
  tipping_range = seq(0.05, 1, by = 0.05),
  cox_fit = NULL,
  verbose = FALSE,
  seed = 12345
)
```

Arguments

dat	data.frame containing at least 5 columns: TRT01P (treatment arm as factor), AVAL (survival time), EVENT (event indicator), CNSRRS (censoring reason) and MAXAVAL (maximum potential survival time, duration between randomization to data cut-off)
reason	Vector specifying censoring reasons to be imputed.
impute	a string specifying the treatment arm(s) which require imputation. It must be one of the arms from variable TRT01P, the first level of TRT01P is considered as the control arm.
imputation_model	used to fit model to observed data (should be "Weibull" or "exponential")
J	numeric indicating number of imputations.
tipping_range	Numeric vector. Hazard inflation (>1) for treatment arm imputation or deflation (<1) range for control arm imputation.
cox_fit	A Cox model that will be used to calculate HRs on imputed datasets. In case of inclusion of stratification factors or covariates, conditional HR will be used.
verbose	Logical. If TRUE, prints progress and analysis details.
seed	Integer. Random seed for reproducibility.

Details

The **model-based tipping point analysis** provides a reproducible and intuitive framework for exploring the robustness of treatment effects in time-to-event (survival) endpoints when censoring may differ between study arms.

A parametric survival model is fitted using maximum likelihood. This function applies a hazard deflation on control arm or hazard inflation on treatment arm, and impute survival times based on the parametric model with additional sampling of the parameters from a multivariate normal distribution. This imputation procedure is iterated across a range of tipping point parameters tipping_range. For each parameter value:

1. Multiple imputed datasets are generated (J replicates), where censored observations in the selected arm are reassigned event times according to the imputation method.
2. A Cox proportional hazards model is fitted to each imputed dataset.
3. Model estimates are pooled using **Rubin's rules** to obtain a combined hazard ratio and confidence interval for that tipping point parameter.

The process yields a series of results showing how the treatment effect changes as increasingly conservative or optimistic assumptions are made about censored observations. The *tipping point* is defined as the smallest value (hazard inflation) or biggest value (hazard deflation) of the sensitivity parameter for which the upper bound of the hazard ratio confidence interval crosses 1 - i.e., where the apparent treatment benefit is lost.

Value

A `tipse` object containing:

original data Input argument from 'data'.

imputation_results A data frame of combined pooled model results across tipping points

original_HR The original hazard ratio.

reason_to_impute Input argument from 'reason'.

arm_to_impute Input argument from 'impute'.

method_to_impute Input argument from 'method'.

imputation_data A list of imputed datasets for each tipping point value.

References

Atkinson, A., Kenward, M. G., Clayton, T., & Carpenter, J. R. (2019). Reference-based sensitivity analysis for time-to-event data. Pharmaceutical statistics, 18(6), 645-658.

Examples

```
cox1 <- survival::coxph(Surv(AVAL, EVENT) ~ TRT01P, data = codebreak200)
result <- tipping_point_model_based(
  dat = codebreak200,
  reason = "Early dropout",
  impute = "docetaxel",
  imputation_model = "weibull",
  J = 10,
  tipping_range = seq(0.1, 1, by = 0.05),
  cox_fit = cox1,
  verbose = TRUE,
  seed = 12345
)
```

`tipping_point_model_free`

Tipping Point Analysis (Model-Free)

Description

Performs a model-free tipping point analysis on time-to-event data by repeatedly imputing censored observations under varying assumptions. The model-free framework assumes that censored patients share similar survival behavior with those from whom they are sampled, without fitting any parametric survival model.

Usage

```
tipping_point_model_free(
  dat,
  reason,
  impute,
  J = 10,
  tipping_range = seq(5, 95, by = 5),
  cox_fit = NULL,
  verbose = FALSE,
  method = c("random sampling", "deterministic sampling"),
  seed = 12345
)
```

Arguments

dat	data.frame containing at least 5 columns: TRT01P (treatment arm as factor), AVAL (survival time), EVENT (event indicator), CNSRRS (censoring reason) and MAXAVAL (maximum potential survival time, duration between randomization to data cut-off)
reason	Vector specifying censoring reasons to be imputed.
impute	a string specifying the treatment arm(s) which require imputation. It must be one of the arms from variable TRT01P, the first level of TRT01P is considered as the control arm.
J	numeric indicating number of imputations.
tipping_range	Numeric vector. Percentiles to use when method = "random sampling". Number of patients to impute when method = "deterministic sampling".
cox_fit	A Cox model that will be used to calculate HRs on imputed datasets. In case of inclusion of stratification factors or covariates, conditional HR will be used.
verbose	Logical. If TRUE, prints progress and analysis details.
method	Character. Either "random sampling" or "deterministic sampling".
seed	Integer. Random seed for reproducibility.

Details

The **model-free tipping point analysis** provides a reproducible and intuitive framework for exploring the robustness of treatment effects in time-to-event (survival) endpoints when censoring may differ between study arms.

Two sampling modes are supported:

- method = "random sampling" - performs re-sampling of event times from the best or worst percentile of observed patients ranked by their event or censoring time. The tipping_range specifies the percentiles of the observed data from which event times will be sampled to impute censored patients. For the treatment arm, use the worst percentiles (shortest survival times) from the observed data of both arms. For the control arm, use the best percentiles (longest survival times).

- `method = "deterministic sampling"` - imputes a fixed number of censored patients deterministically. The `tipping_range` specifies the number of patients to be imputed. For the treatment arm, it defines the number of patients that will be assumed to have an event at their time of censoring. For the control arm, it defines the number of patients that will be assumed to be event-free at data cut-off, their maximum potential follow-up time.

This function iteratively applies the random- or deterministic-sampling imputation procedure across a range of tipping point parameters `tipping_range`. For each parameter value:

1. Multiple imputed datasets are generated (`J` replicates), where censored observations in the selected arm are replaced by sampled or reassigned event times according to the imputation method.
2. A Cox proportional hazards model is fitted to each imputed dataset.
3. Model estimates are pooled using **Rubin's rules** to obtain a combined hazard ratio and confidence interval for that tipping point parameter.

The process yields a series of results showing how the treatment effect changes as increasingly conservative or optimistic assumptions are made about censored observations. The *tipping point* is defined as the smallest value of the sensitivity parameter (percentile or number of imputed patients) for which the upper bound of the hazard ratio confidence interval crosses 1 - i.e., where the apparent treatment benefit is lost.

Value

A `tipse` object containing:

original data Input argument from 'data'.

imputation_results A data frame of combined pooled model results across tipping points

original_HR The original hazard ratio.

reason_to_impute Input argument from 'reason'.

arm_to_impute Input argument from 'impute'.

method_to_impute Input argument from 'method'.

imputation_data A list of imputed datasets for each tipping point value.

Examples

```
cox1 <- survival::coxph(Surv(AVAL, EVENT) ~ TRT01P, data = codebreak200)
result <- tipping_point_model_free(
  dat = codebreak200,
  reason = "Early dropout",
  impute = "docetaxel",
  J = 10,
  tipping_range = seq(5, 95, by = 5),
  cox_fit = cox1,
  verbose = TRUE,
  method = "random sampling",
  seed = 12345
)
```

```
result2 <- tipping_point_model_free(
  dat = codebreak200,
  reason = "Early dropout",
  impute = "docetaxel",
  J = 10,
  tipping_range = seq(1, 21, by = 2),
  cox_fit = cox1,
  verbose = TRUE,
  method = "deterministic sampling",
  seed = 12345
)
```

Index