

Package ‘CopulaCenR’

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Type Package

Title Copula-Based Regression Models for Multivariate Censored Data

Version 1.2.4

Description Copula-based regression models for multivariate censored data, including bivariate right-censored data, bivariate interval-censored data, and right/interval-censored semi-competing risks data. Currently supports Clayton, Gumbel, Frank, Joe, AMH and Copula2 copula models. For marginal models, it supports parametric (Weibull, Loglogistic, Gompertz) and semiparametric (Cox and transformation) models. Includes methods for convenient prediction and plotting. Also provides a bivariate time-to-event simulation function and an information ratio-based goodness-of-fit test for copula. Method details can be found in Sun et.al (2019) Lifetime Data Analysis, Sun et.al (2021) Biostatistics, Sun et.al (2022) Statistical Methods in Medical Research, Sun et.al (2022) Biometrics, and Sun et al. (2023+) JRSSC.

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 ACTG181

 ACTG181

Description

An example real dataset of bivariate interval-censored data with 204 subjects and one covariate. The data come from the AIDS Clinical Trials Group protocol ACTG 181. Two events are the shedding time (in months) of cytomegalovirus (CMV) in urine/blood and the colonization time (in months) of mycobacterium avium complex (MAC) in sputum/stool (Betensky and Finkelstein, 1999).

Usage

```
data("ACTG181")
```

Format

A data frame with 408 observations on the following 6 variables.

`id` subject id

`ind` margin indicator, 1=shedding time, 2=colonization time

`Left` left bound of observed interval

`Right` right bound of observed interval

`status` censoring indicator; 1=interval-censor, 0=right censor. All observations are interval-censored in this dataset

`x` covariate

Source

Betensky and Finkelstein (1999). A non-parametric maximum likelihood estimator for bivariate interval censored data. *Statistics in Medicine* **18** 3089-3100.

Examples

```
data(ACTG181)
clayton_sp <- ic_spTran_copula(data = ACTG181,
                             copula = "Clayton",
                             l = 0, u = 25,
                             r = 3, m = 3,
                             var_list = "x")
summary(clayton_sp)
```

AIC.CopulaCenR *the AIC of a CopulaCenR object*

Description

the AIC of a CopulaCenR object

Usage

```
## S3 method for class 'CopulaCenR'
AIC(object, ..., k = 2)
```

Arguments

<code>object</code>	a CopulaCenR object
<code>...</code>	further arguments
<code>k</code>	numeric, with <code>k = 2</code> for AIC

AREDS

*AREDS***Description**

A real dataset of bivariate interval-censored data with 629 subjects and 4 non-genetic covariates and 1 genetic covariate. The dataset is selected from the Age-related Eye Disease Study (AREDS) (AREDS Group, 1999). Two events are the progression times (in years) to late-AMD in the left and right eyes.

Usage

```
data("AREDS")
```

Format

A data frame with 1258 observations (629 subjects with 2 eyes) on the following 8 variables.

`id` subject id

`ind` margin indicator, 1=left eye, 2=right eye

`Left` left bound of observed interval

`Right` right bound of observed interval

`status` censoring indicator; 1=interval-censor, 0=right censor.

`SevScaleBL` baseline AMD severity score, margin-specific

`ENROLLAGE` age at baseline

`rs2284665` a SNP covariate highly associated with late-AMD progression, coded as 0,1,2

Source

AREDS Group (1999). The Age-Related Eye Disease Study (AREDS): design implications. AREDS report no. 1. *Control Clinical Trials* **20**, 573-600.

Examples

```
data(AREDS)
copula2_sp <- ic_spTran_copula(data = AREDS,
  copula = "Copula2",
  var_list = c("ENROLLAGE",
    "rs2284665",
    "SevScaleBL"),
  l = 0, u = 15, m = 3, r = 3)
summary(copula2_sp)
```

BIC.CopulaCenR	<i>the BIC of a CopulaCenR object</i>
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Description

the BIC of a CopulaCenR object

Usage

```
## S3 method for class 'CopulaCenR'  
BIC(object, ...)
```

Arguments

object	a CopulaCenR object
...	further arguments

coef.CopulaCenR	<i>the coefficient estimates of a CopulaCenR object</i>
-----------------	---

Description

the coefficient estimates of a CopulaCenR object

Usage

```
## S3 method for class 'CopulaCenR'  
coef(object, ...)
```

Arguments

object	a CopulaCenR object
...	further arguments

Description

Bivariate time-to-event data frequently arise in research areas such as clinical trials and epidemiological studies, where the occurrence of two events are correlated. In many cases, the exact event times are unknown due to censoring. Specifically, bivariate right-censored data occur when the study ends prior to the occurrence of one or both events. In another situation, bivariate interval-censored data occur when the status of both events are periodically examined at intermittent assessment times. In this case, the right censoring could also happen if the event still does not occur at the last assessment time. A special case of interval-censored data is the current status data if there is only one assessment time and the event is only known to occur or not by its assessment time.

The copula model is a popular approach for modeling correlated bivariate censored data. One unique feature of copula is that it models the two marginal distributions and the between-margin dependence separately, allowing flexibility in marginal models and straightforward interpretation for covariate effects. Moreover, the challenge from censoring can be naturally handled through the marginal distributions within the copula function. Besides, the joint, marginal and conditional distributions can be obtained based on the copula model. However, there is a lack of R package implementing copula-based regression models for bivariate data under both right- and interval-censoring.

The CopulaCenR package can build copula-based regression models for both bivariate right-censored data and bivariate interval-censored data (including the special case of bivariate current status data). The package is flexible in terms of various built-in Archimedean copulas (such as Clayton, Gumbel, Frank, Joe, AMH), together with a two-parameter copula (Copula2) that incorporates the popular Clayton and Gumbel copulas as special cases. It also allows a broad class of marginal distributions, including parametric (i.e., Weibull, Gompertz, Loglogistic) and semiparametric (i.e., unspecified functions, such as Cox, transformation) margins.

The main features of CopulaCenR are:

- (1) Copula models with parametric margins: `rc_par_copula` and `ic_par_copula`) for bivariate right-censored data and bivariate interval-censored data, respectively.
- (2) Copula models with semiparametric margins: `rc_spCox_copula` and `ic_spTran_copula`) for bivariate right-censored data and bivariate interval-censored data, respectively.
- (3) Wald (performed during model fitting), score (`score_copula`) and likelihood-ratio (`lrt_copula`) tests for covariate effects.
- (4) Calculate Kendall's tau from a fitted model: `tau_copula`.
- (5) Calculate other model parameters using S3 methods: `print`, `summary`, `coef`, `logLik`, `AIC`, `BIC`.

(6) Extract fitted values (such as linear predictors and survival probabilities) from a fitted model: `fitted`.

(7) Predict in new observations (such as linear predictors and survival probabilities) from a fitted model: `predict`.

(8) Plot joint, conditional and marginal survival probability profiles for given subjects based on a fitted model: `plot`, `lines`.

(9) A user-friendly function to simulate bivariate event times: `data_sim_copula`.

Source

Tao Sun, Yi Liu, Richard J. Cook, Wei Chen and Ying Ding (2018). Copula-based Score Test for Bivariate Time-to-event Data, with Application to a Genetic Study of AMD Progression. #' *Life-time Data Analysis* 25(3), 546-568.

Tao Sun and Ying Ding (In Press). Copula-based Semiparametric Regression Method for Bivariate Data under General Interval Censoring. <http://arxiv.org/abs/1901.01918>.

Examples

```
### bivariate right-censored data
data(DRS)
# fit a Clayton-Weibull model
clayton_wb <- rc_par_copula(data = DRS,
                           var_list = "treat",
                           copula = "Clayton",
                           m.dist = "Weibull")
summary(clayton_wb)

### bivariate interval-censored data
data(AREDS)
copula2_sp <- ic_spTran_copula(data = AREDS,
                              copula = "Copula2", l = 0, u = 15,
                              m = 3, r = 3, var_list =
                                c("ENROLLAGE", "rs2284665",
                                  "SevScaleBL"))
summary(copula2_sp)
```

Description

A simulated real dataset of interval-censored semi-competing risks data with 500 subjects and 10 columns.

Usage

```
data("data_scmprisk")
```

Format

A data frame with 500 subjects on the following 10 variables.

id subject id

Left left bound of observed interval of non-terminal event

Right right bound of observed interval of non-terminal event

status censoring indicator of non-terminal event; 1=interval-censor, 0=right censor.

timeD observed time of non-terminal event

statusD censoring indicator of terminal event; 1=interval-censor, 0=right censor.

A study entry time (i.e., left truncation time).

x1 first covariate

x2 second covariate

x3 third covariate

data_scmprisk_rc

data_scmprisk_rc

Description

A simulated real dataset of right-censored semi-competing risks data with 150 subjects and 7 columns.

Usage

```
data("data_scmprisk_rc")
```

Format

A data frame with 150 subjects on the following 7 variables.

time1 time to non-terminal event

event1 0 for right-censoring, 1 for event1

time2 observed terminal event time

event2 0 for right-censoring, 1 for event2

x1 first covariate

x2 second covariate

x3 third covariate

data_sim_copula	<i>Simulate bivariate time-to-event times based on specific copula and marginal distributions</i>
-----------------	---

Description

To generate a sample of subjects with two correlated event times based on specific copula and marginal models

Usage

```
data_sim_copula(n, copula, eta, dist, baseline, var_list, COV_beta, x1, x2)
```

Arguments

n	sample size
copula	types of copula, including "Clayton", "Gumbel", "Frank", "AMH", "Joe"
eta	copula parameter η
dist	marginal distributions, including "Weibull", "Gompertz", "Loglogistic"
baseline	marginal distribution parameters. For Weibull and Loglogistic, it shall be λ (scale) and k (shape); for Gompertz, it shall be a (shape) and b (rate)
var_list	a vector of covariate names; assume the same covariates for two margins
COV_beta	a vector of regression coefficients corresponding to var_list; assume the same coefficients between two margins
x1	a data frame of covariates for margin 1; it shall have n rows, with columns corresponding to the var_list
x2	a data frame of covariates for margin 2

Details

The parametric generator functions of copula functions are list below:

The Clayton copula has a generator

$$\phi_{\eta}(t) = (1 + t)^{-1/\eta},$$

with $\eta > 0$ and Kendall's $\tau = \eta/(2 + \eta)$.

The Gumbel copula has a generator

$$\phi_{\eta}(t) = \exp(-t^{1/\eta}),$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 1/\eta$.

The Frank copula has a generator

$$\phi_{\eta}(t) = -\eta^{-1} \log\{1 + e^{-t}(e^{-\eta} - 1)\},$$

with $\eta \geq 0$ and Kendall's $\tau = 1 + 4\{D_1(\eta) - 1\}/\eta$, in which $D_1(\eta) = \frac{1}{\eta} \int_0^\eta \frac{t}{e^t - 1} dt$.

The AMH copula has a generator

$$\phi_\eta(t) = (1 - \eta)/(e^t - \eta),$$

with $\eta \in [0, 1)$ and Kendall's $\tau = 1 - 2\{(1 - \eta)^2 \log(1 - \eta) + \eta\}/(3\eta^2)$.

The Joe copula has a generator

$$\phi_\eta(t) = 1 - (1 - e^{-t})^{1/\eta},$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 4 \sum_{k=1}^{\infty} \frac{1}{k(\eta k + 2)\{\eta(k-1) + 2\}}$.

The marginal survival distributions are listed below:

The Weibull (PH) survival distribution is

$$\exp\{-(t/\lambda)^k e^{Z^\top \beta}\},$$

with $\lambda > 0$ as scale and $k > 0$ as shape.

The Gompertz (PH) survival distribution is

$$\exp\left\{-\frac{b}{a}(e^{at} - 1)e^{Z^\top \beta}\right\},$$

with $a > 0$ as shape and $b > 0$ as rate

The Loglogistic (PO) survival distribution is

$$\{1 + (t/\lambda)^k e^{Z^\top \beta}\}^{-1},$$

with $\lambda > 0$ as scale and $k > 0$ as shape.

Value

a data frame of bivariate time-to-event data with covariates

Examples

```
library(CopulaCenR)
set.seed(1)
dat <- data_sim_copula(n = 500, copula = "Clayton", eta = 3,
  dist = "Weibull", baseline = c(0.1, 2),
  var_list = c("var1", "var2"),
  COV_beta = c(0.1, 0.1),
  x1 = cbind(rnorm(500, 6, 2),
    rbinom(500, 1, 0.5)),
  x2 = cbind(rnorm(500, 6, 2),
    rbinom(500, 1, 0.5)))
plot(x = dat$time[dat$ind == 1], y = dat$time[dat$ind == 2],
  xlab = expression(t[1]), ylab = expression(t[2]),
  cex.axis = 1, cex.lab = 1.3)
```

data_sim_ic	<i>data_sim_ic</i>
-------------	--------------------

Description

A simulated real dataset of bivariate interval-censored data with 500 subjects and 7 columns.

Usage

```
data("data_sim_ic")
```

Format

A data frame with 500 subjects on the following 7 variables.

id subject id

Left.L left bound of the first event

Right.L right bound of the first event

status.L censoring indicator of the first event; 1=interval censor, 0=right censor.

Left.R left bound of the second event

Right.R right bound of the second event

status.R censoring indicator of the second event; 1=interval censor, 0=right censor.

data_sim_multi_rec	<i>data_sim_multi_rec</i>
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Description

A simulated real dataset of multivariate recurrent events data with 300 subjects.

Usage

```
data("data_sim_multi_rec")
```

Format

A list with 300 subjects on the following 2 components.

gaptimes a data frame with 300 subjects in row and 4 gap times in column

status a data frame with 300 subjects in row and 4 statuses in column

`data_sim_RC`*data_sim_RC*

Description

A simulated real dataset of bivariate right-censored data with 500 subjects and 5 columns.

Usage

```
data("data_sim_RC")
```

Format

A data frame with 500 subjects on the following 5 variables.

`id` subject id

`event_time.L` observed time of the first event

`status.L` censoring indicator of the first event; 1=exactly observed, 0=right censor.

`event_time.R` observed time of the second event

`status.R` censoring indicator of the second event; 1=exactly observed, 0=right censor.

`data_sim_rec`*data_sim_rec*

Description

A simulated real dataset of bivariate recurrent events data with 500 subjects and 6 columns.

Usage

```
data("data_sim_rec")
```

Format

A data frame with 500 subjects on the following 6 variables.

`id` subject id

`gap1` observed time of the first gap time

`status1` censoring indicator of the first event; 1=exactly observed, 0=right censor.

`gap2` observed time of the second gap time

`status2` censoring indicator of the second event; 1=exactly observed, 0=right censor.

`d` cluster size

data_sim_scmprisk_vs *data_sim_scmprisk_vs*

Description

A simulated real dataset of bivariate time-to-event data based on specific copula and marginal distributions with 500 subjects and 10 columns.

Usage

```
data("data_sim_scmprisk_vs")
```

Format

A data frame with 500 subjects on the following 10 variables.

id subject id
ind 1,2 for two margins
x1 first covariate
x2 second covariate
x3 third covariate
x4 fourth covariate
x5 fifth covariate
time time to event
obs_time observed time
status 0 for right-censoring, 1 for event

DRS

DRS

Description

A real dataset of bivariate right-censored data with 197 subjects and 3 covariates. The patients were a 50% random sample of the patients with "high-risk" diabetic retinopathy as defined by the Diabetic Retinopathy Study (DRS) (Huster, 1989).

Usage

```
data("DRS")
```

Format

A data frame with 394 observations on the following 7 variables.

id subject id
 ind margin indicator, 1 for right eye, 2 for left eye
 obs_time time of blindness (in months) from treatment
 status censoring indicator, 1 = blindness, 0 = right censoring
 treat laser treatment type, 0 = no treatment, 1 = xenon, 2 = argon
 age age at diagnosis of diabetes
 type type of diabetes, 1 = juvenile (age at treatment < 20), 2 = adult

Details

Each patient had one eye randomized to laser treatment and the other eye received no treatment. For each eye, the event of interest was the time from initiation of treatment to the time when visual acuity dropped below 5/200 (call it "blindness"). Survival times in this dataset are the actual time to blindness in months. Censoring was caused by death, dropout, or end of the study.

Source

<https://www.mayo.edu/research/documents/DRShtml/DOC-10027460>

References

Huster WJ, Brookmeyer R, Self SG (1989). Modeling paired survival data with covariates. *Biometrics* **45**, 145-156.

Examples

```
data(DRS)
clayton_wb <- rc_par_copula(data = DRS,
  var_list = "treat",
  copula = "Clayton",
  m.dist = "Weibull")
summary(clayton_wb)
```

fitted.CopulaCenR

Fitted values from CopulaCenR regression models

Description

Fitted values based on models from `ic_spTran_copula`, `rc_spCox_copula`, `ic_par_copula` and `rc_par_copula`.

Usage

```
## S3 method for class 'CopulaCenR'
fitted(object, type = "lp", ...)
```

Arguments

object	a CopulaCenR object from ic_spTran_copula, rc_spCox_copula, ic_par_copula and rc_par_copula
type	"lp" for linear predictors or "survival" for marginal and joint survival probabilities
...	further arguments

Details

When the argument `type = "lp"`, it gives a linear predictor for each margin (i.e., log hazards ratio in the proportional hazards model, log proportional odds in the proportional odds model).

When the argument `type = "survival"` and the fitted data is bivariate right-censored, the marginal and joint survival values will be evaluated at the observed times. For bivariate interval-censored, evaluation times are the interval middle points or left bound (if right bound is infinity).

Value

If `type = "lp"`, it returns a data frame with `id`, `lp1` (linear predictor for margin 1), `lp2`. If `type = "survival"`, it returns a data frame with `id`, `t1` (evaluated times for the margin 1), `t2`, `S1` (predicted marginal survival probabilities for margin 1), `S2` and `S12` (the predicted joint survival probabilities)

Examples

```
data(AREDS)
# fit a Copula2-Sieve model
copula2_sp <- ic_spTran_copula(data = AREDS, copula = "Copula2",
                             l = 0, u = 15, m = 3, r = 3,
                             var_list = c("ENROLLAGE", "rs2284665", "SevScaleBL"))
output <- fitted(object = copula2_sp)
```

ic_par_copula	<i>Copula regression models with parametric margins for bivariate interval-censored data</i>
---------------	--

Description

Fits a copula model with parametric margins for bivariate interval-censored data.

Usage

```
ic_par_copula(
  data,
  var_list,
  copula,
  m.dist = "Weibull",
  method = "BFGS",
  iter = 300,
  stepsize = 1e-05,
  hes = TRUE,
  control = list()
)
```

Arguments

data	a data frame; must have id (subject id), ind (1,2 for two units in each subject), Left (0 if left-censoring), Right (Inf if right-censoring), status (0 for right-censoring, 1 for interval-censoring or left-censoring), and covariates by column.
var_list	the list of covariates to be fitted into the copula model.
copula	Types of copula model.
m.dist	baseline marginal distribution.
method	optimization method (see ?optim); default is "BFGS"; also can be "Newton" (see ?nlm).
iter	number of iterations when method is "Newton"; default is 300.
stepsize	size of optimization step when method is "Newton"; default is 1e-5.
hes	default is TRUE for hessian calculation.
control	a list of control parameters for methods other than "Newton"; see ?optim.

Details

The input data must be a data frame. with columns id (sample id), ind (1,2 for the two units from the same id), Left (0 if left-censoring), Right (Inf if right-censoring), status (0 for right-censoring, 1 for interval-censoring or left-censoring), and covariates. The function does not allow Left == Right.

The supported copula models are "Clayton", "Gumbel", "Frank", "AMH", "Joe" and "Copula2". The "Copula2" model is a two-parameter copula model that incorporates Clayton and Gumbel as special cases. The parametric generator functions of copula functions are list below:

The Clayton copula has a generator

$$\phi_{\eta}(t) = (1 + t)^{-1/\eta},$$

with $\eta > 0$ and Kendall's $\tau = \eta/(2 + \eta)$.

The Gumbel copula has a generator

$$\phi_{\eta}(t) = \exp(-t^{1/\eta}),$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 1/\eta$.

The Frank copula has a generator

$$\phi_\eta(t) = -\eta^{-1} \log\{1 + e^{-t}(e^{-\eta} - 1)\},$$

with $\eta \geq 0$ and Kendall's $\tau = 1 + 4\{D_1(\eta) - 1\}/\eta$, in which $D_1(\eta) = \frac{1}{\eta} \int_0^\eta \frac{t}{e^t - 1} dt$.

The AMH copula has a generator

$$\phi_\eta(t) = (1 - \eta)/(e^t - \eta),$$

with $\eta \in [0, 1)$ and Kendall's $\tau = 1 - 2\{(1 - \eta)^2 \log(1 - \eta) + \eta\}/(3\eta^2)$.

The Joe copula has a generator

$$\phi_\eta(t) = 1 - (1 - e^{-t})^{1/\eta},$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 4 \sum_{k=1}^{\infty} \frac{1}{k(\eta k + 2)\{\eta(k-1) + 2\}}$.

The Two-parameter copula (Copula2) has a generator

$$\phi_\eta(t) = \{1/(1 + t^\alpha)\}^\kappa,$$

with $\alpha \in (0, 1]$, $\kappa > 0$ and Kendall's $\tau = 1 - 2\alpha\kappa/(2\kappa + 1)$.

The supported marginal distributions are "Weibull" (proportional hazards), "Gompertz" (proportional hazards) and "Loglogistic" (proportional odds). These marginal distributions are listed below and we assume the same baseline parameters between two margins.

The Weibull (PH) survival distribution is

$$\exp\{-(t/\lambda)^k e^{Z^T \beta}\},$$

with $\lambda > 0$ as scale and $k > 0$ as shape.

The Gompertz (PH) survival distribution is

$$\exp\{-\frac{b}{a}(e^{at} - 1)e^{Z^T \beta}\},$$

with $a > 0$ as shape and $b > 0$ as rate.

The Loglogistic (PO) survival distribution is

$$\{1 + (t/\lambda)^k e^{Z^T \beta}\}^{-1},$$

with $\lambda > 0$ as scale and $k > 0$ as shape.

Optimization methods can be all methods (except "Brent") from `optim`, such as "Nelder-Mead", "BFGS", "CG", "L-BFGS-B", "SANN". Users can also use "Newton" (from `nlm`).

Value

a `CopulaCenR` object summarizing the model. Can be used as an input to general S3 methods including `summary`, `print`, `plot`, `lines`, `coef`, `logLik`, `AIC`, `BIC`, `fitted`, `predict`.

Source

Tao Sun, Yi Liu, Richard J. Cook, Wei Chen and Ying Ding (2019). Copula-based Score Test for Bivariate Time-to-event Data, with Application to a Genetic Study of AMD Progression. *Lifetime Data Analysis* 25(3), 546-568.

Tao Sun and Ying Ding (In Press). Copula-based Semiparametric Regression Model for Bivariate Data under General Interval Censoring. *Biostatistics*. DOI: 10.1093/biostatistics/kxz032.

Examples

```
# fit a Copula2-Weibull model
data(AREDS)
copula2_wb <- ic_par_copula(data = AREDS, copula = "Copula2",
                           m.dist = "Weibull",
                           var_list = c("ENROLLAGE", "rs2284665"))
summary(copula2_wb)
```

ic_scmprisk_spTran_copula

Copula regression models with semi-parametric transformation margins for semi-competing risk data under interval-censoring and left-truncation

Description

Fits a copula model with semi-parametric transformation margins for semi-competing risk data under interval-censoring and left-truncation.

Usage

```
ic_scmprisk_spTran_copula(
  data,
  var_list,
  copula = "Copula2",
  l1 = 0,
  u1,
  m1 = 3,
  r1 = 1,
  l2 = 0,
  u2,
  m2 = 3,
  r2 = 1,
  method = "BFGS",
  iter = 1000,
  stepsize = 1e-05,
  control = list(),
  eta_ini = NULL
)
```

Arguments

data	a data frame; must have id (subject id), Left (0 if left-censoring for non-terminal event), Right (Inf if right-censoring for non-terminal event), status (0 for right-censoring, 1 for interval-censoring or left-censoring of non-terminal event), timeD (observed terminal event), statusD (for terminal event), A (left truncation time, 0 if none), and covariates by column.
var_list	the list of covariates to be fitted into the copula model.
copula	Types of copula model, only Copula2 is supported at this stage.
l1	for non-terminal event, the left bound for all Left and Right endpoints of observed finite intervals; default is 0.
u1	for non-terminal event, the right bound for all Left and Right endpoints of observed finite intervals; has to be a finite value
m1	for non-terminal event, integer, degree of Bernstein polynomials for both margins; default is 3
r1	for non-terminal event, positive transformation parameter for the semiparametric transformation marginal model.
l2	for terminal event, the left bound for all Left and Right endpoints of observed finite intervals; default is 0.
u2	for terminal event, the right bound for all Left and Right endpoints of observed finite intervals; has to be a finite value
m2	for terminal event, integer, degree of Bernstein polynomials for both margins; default is 3
r2	for terminal event, positive transformation parameter for the semiparametric transformation marginal model.
method	optimization method (see ?optim); default is "BFGS"; also can be "Newton" (see ?nlm).
iter	number of iterations when method is "Newton"; default is 300.
stepsize	size of optimization step when method is "Newton"; default is 1e-5.
control	a list of control parameters for methods other than "Newton"; see ?optim.
eta_ini	a vector of initial values for copula parameters, default is NULL

Details

The input data must be a data frame. with columns id (sample id), Left (0 if left-censoring), Right (Inf if right-censoring), status (0 for right-censoring, 1 for interval-censoring or left-censoring), timeD (for terminal event), statusD,A (0 if no left truncation), and covariates. The function does not allow Left == Right.

The supported copula model in this version is "Copula2". The "Copula2" model is a two-parameter copula model that incorporates Clayton and Gumbel as special cases. The parametric generator functions of copula functions are list below:

The Two-parameter copula (Copula2) has a generator

$$\phi_{\eta}(t) = \{1/(1 + t^{\alpha})\}^{\kappa},$$

with $\alpha \in (0, 1]$, $\kappa > 0$ and Kendall's $\tau = 1 - 2\alpha\kappa/(2\kappa + 1)$.

The marginal semiparametric transformation models are built based on Bernstein polynomials, which is formulated below:

$$S(t|Z) = \exp[-G\{\Lambda(t)e^{Z^T\beta}\}],$$

where t is time, Z is covariate, β is coefficient and $\Lambda(t)$ is an unspecified function with infinite dimensions. We approximate $\Lambda(t)$ in a sieve space constructed by Bernstein polynomials with degree m . By default, $m = 3$. In the end, all model parameters are estimated by the sieve estimators (Sun and Ding, In Press).

The $G(\cdot)$ function is the transformation function with a parameter $r > 0$, which has a form of $G(x) = \frac{(1+x)^r - 1}{r}$, when $0 < r \leq 2$ and $G(x) = \frac{\log\{1+(r-2)x\}}{r-2}$ when $r > 2$. When $r = 1$, the marginal model becomes a proportional hazards model; when $r = 3$, the marginal model becomes a proportional odds model. In practice, m and r can be selected based on the AIC value.

Optimization methods can be all methods (except "Brent") from `optim`, such as "Nelder-Mead", "BFGS", "CG", "L-BFGS-B", "SANN". Users can also use "Newton" (from `nlm`).

Value

a `CopulaCenR` object summarizing the model. Can be used as an input to general S3 methods including `summary`, `print`, `coef`, `logLik`, `AIC`, `BIC`.

Source

Tao Sun, Yunlong Li, Zhengyan Xiao, Ying Ding, Xiaojun Wang (2022). Semiparametric copula method for semi-competing risks data subject to interval censoring and left truncation: Application to disability in elderly. *Statistical Methods in Medical Research* (Accepted).

Examples

```
# fit a Copula2-Semiparametric model
data("data_scmprisk")
copula2_sp <- ic_scmprisk_spTran_copula(data = data_scmprisk,
  var_list = c("x1"), copula = "Copula2",
  l1=0, u1 = 21, m1 = 3, r1 = 1,
  l2=0, u2 = 21, m2 = 3, r2 = 1,
  )
summary(copula2_sp)
```

ic_spTran_copula

Copula regression models with semiparametric margins for bivariate interval-censored data

Description

Fits a copula model with semiparametric margins for bivariate interval-censored data.

Usage

```
ic_spTran_copula(
  data,
  var_list,
  l = 0,
  u,
  copula = "Copula2",
  m = 3,
  r = 3,
  method = "BFGS",
  iter = 300,
  stepsize = 1e-06,
  hes = TRUE,
  control = list()
)
```

Arguments

data	a data frame; must have id (subject id), ind (1,2 for two units in each subject), Left (0 if left-censoring), Right (Inf if right-censoring), status (0 for right-censoring, 1 for interval-censoring or left-censoring), and covariates by column.
var_list	the list of covariates to be fitted into the copula model.
l	the left bound for all Left and Right endpoints of observed finite intervals; default is 0.
u	the right bound for all Left and Right endpoints of observed finite intervals; has to be a finite value
copula	Types of copula model.
m	integer, degree of Bernstein polynomials for both margins; default is 3
r	postive transformation parameter for the semiparametric transformation marginal model.
method	optimization method (see ?optim); default is "BFGS"; also can be "Newton" (see ?nlm).
iter	number of iterations when method = "Newton"; default is 300.
stepsize	size of optimization step when method is "Newton"; default is 1e-6.
hes	default is TRUE for hessian calculation; if LRT is desired, can set hes = FALSE to save time.
control	a list of control parameters for methods other than "Newton"; see ?optim.

Details

The input data must be a data frame. with columns id (sample id), ind (1,2 for the two units from the same id), Left (0 if left-censoring), Right (Inf if right-censoring), status (0 for right-censoring, 1 for interval-censoring or left-censoring), and covariates. The function does not allow

Left == Right.

The supported copula models are "Clayton", "Gumbel", "Frank", "AMH", "Joe" and "Copula2". The "Copula2" model is a two-parameter copula model that incorporates Clayton and Gumbel as special cases. The parametric generator functions of copula functions are list below:

The Clayton copula has a generator

$$\phi_{\eta}(t) = (1 + t)^{-1/\eta},$$

with $\eta > 0$ and Kendall's $\tau = \eta/(2 + \eta)$.

The Gumbel copula has a generator

$$\phi_{\eta}(t) = \exp(-t^{1/\eta}),$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 1/\eta$.

The Frank copula has a generator

$$\phi_{\eta}(t) = -\eta^{-1} \log\{1 + e^{-t}(e^{-\eta} - 1)\},$$

with $\eta \geq 0$ and Kendall's $\tau = 1 + 4\{D_1(\eta) - 1\}/\eta$, in which $D_1(\eta) = \frac{1}{\eta} \int_0^{\eta} \frac{t}{e^t - 1} dt$.

The AMH copula has a generator

$$\phi_{\eta}(t) = (1 - \eta)/(e^t - \eta),$$

with $\eta \in [0, 1)$ and Kendall's $\tau = 1 - 2\{(1 - \eta)^2 \log(1 - \eta) + \eta\}/(3\eta^2)$.

The Joe copula has a generator

$$\phi_{\eta}(t) = 1 - (1 - e^{-t})^{1/\eta},$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 4 \sum_{k=1}^{\infty} \frac{1}{k(\eta k + 2)\{\eta(k-1) + 2\}}$.

The Two-parameter copula (Copula2) has a generator

$$\phi_{\eta}(t) = \{1/(1 + t^{\alpha})\}^{\kappa},$$

with $\alpha \in (0, 1]$, $\kappa > 0$ and Kendall's $\tau = 1 - 2\alpha\kappa/(2\kappa + 1)$.

The marginal semiparametric transformation models are built based on Bernstein polynomials, which is formulated below:

$$S(t|Z) = \exp[-G\{\Lambda(t)e^{Z^T \beta}\}],$$

where t is time, Z is covariate, β is coefficient and $\Lambda(t)$ is an unspecified function with infinite dimensions. We approximate $\Lambda(t)$ in a sieve space constructed by Bernstein polynomials with degree m . By default, $m = 3$. In the end, all model parameters are estimated by the sieve estimators (Sun and Ding, In Press).

The $G(\cdot)$ function is the transformation function with a parameter $r > 0$, which has a form of $G(x) = \frac{(1+x)^r - 1}{r}$, when $0 < r \leq 2$ and $G(x) = \frac{\log\{1+(r-2)x\}}{r-2}$ when $r > 2$. When $r = 1$, the marginal model becomes a proportional hazards model; when $r = 3$, the marginal model becomes a proportional odds model. In practice, m and r can be selected based on the AIC value.

Optimization methods can be all methods (except "Brent") from `optim`, such as "Nelder-Mead", "BFGS", "CG", "L-BFGS-B", "SANN". Users can also use "Newton" (from `nlm`).

Value

a CopulaCenR object summarizing the model. Can be used as an input to general S3 methods including summary, print, plot, lines, coef, logLik, AIC, BIC, fitted, predict.

Source

Tao Sun, Yi Liu, Richard J. Cook, Wei Chen and Ying Ding (2019). Copula-based Score Test for Bivariate Time-to-event Data, with Application to a Genetic Study of AMD Progression. *Lifetime Data Analysis* 25(3), 546-568.

Tao Sun and Ying Ding (In Press). Copula-based Semiparametric Regression Model for Bivariate Data under General Interval Censoring. *Biostatistics*. DOI: 10.1093/biostatistics/kxz032.

Examples

```
# fit a Copula2-Semiparametric model
data(AREDS)
copula2_sp <- ic_spTran_copula(data = AREDS, copula = "Copula2",
                             l = 0, u = 15, m = 3, r = 3,
                             var_list = c("ENROLLAGE", "rs2284665", "SevScaleBL"))
summary(copula2_sp)
```

 IRsurv

An information ratio-based goodness-of-fit test for copula models on censored data

Description

Fits an Information ratio (IR)-based goodness-of-fit test for copula models under various censoring types.

Usage

```
IRsurv(
  data,
  censoring = "rc",
  copula = "clayton",
  fams = c(3, 3, 3),
  R = 200,
  parallel = "no",
  ncpus = 1
)
```

Arguments

data the input data; see examples for details.
censoring types of censoring, including "rc", "ic", "rec_bivariate", "rec_multivariate".

copula	specify the copula family to be tested; default is "clayton"; others include "copula2", "gumbel", "frank", "gaussian", and "d-vine". "d-vine" is only for censoring = "rec_multivariate".
fams	specify the unconditional copulas by following the style of the VineCopula package when copula = "d-vine". Only d = 4 is supported at this stage. The conditional copulas are set as "frank" by default.
R	number of Bootstraps; default is 200.
parallel	indicator of parallel computing; can be "no" or "multicore"; default is "no".
ncpus	number of cpus to be assigned for parallel computing; default is 1.

Value

the p value of the IR test

Source

Tao Sun, Yu Cheng, Ying Ding (2022). An information Ratio-based Goodness-of-Fit Test for Copula Models on Censored Data. *Biometrics* (Accepted).

Examples

```
## Not run:
# Goodness of fit under right censoring
data("data_sim_RC")
test_rc <- IRsurv(data = data_sim_RC, censoring = "rc", copula = "clayton", R = 200)
test_rc
# Goodness of fit under interval censoring
data("data_sim_ic")
test_ic <- IRsurv(data = data_sim_ic, censoring = "ic", copula = "clayton", R = 200)
test_ic
# Goodness of fit under bivariate recurrent events
data("data_sim_rec")
test_rec_bi <- IRsurv(data = data_sim_rec, censoring = "rec_bivariate",
                     copula = "clayton", R = 200)
test_rec_bi
# Goodness of fit of D-vine copula under multivariate recurrent events
data("data_sim_multi_rec")
test_rec_mv <- IRsurv(data = data_sim_multi_rec, censoring = "rec_multivariate",
                     fams = c(3,3,3), R = 200)
test_rec_mv

## End(Not run)
```

Kidney

Kidney

Description

A real dataset of bivariate right-censored data with 38 subjects and 3 covariates. The data are the recurrence times to infection, at the point of insertion of the catheter, for kidney patients using portable dialysis equipment. Catheters may be removed for reasons other than infection, in which case the observation is censored. Each patient has exactly 2 observations.

Usage

```
data("Kidney")
```

Format

A data frame with 76 observations on the following 7 variables.

id subject id

ind margin indicator

obs_time observed time

status event status

age in years

sex 1=male, 2=female

disease disease type with 4 levels Other GN AN PKD

Note

This data has often been used to illustrate the use of random effects (frailty) in a survival model. However, one of the males (id 21) is a large outlier, with much longer survival than his peers. If this observation is removed no evidence remains for a random subject effect.

Source

<https://github.com/therneau/survival>

References

CA McGilchrist, CW Aisbett (1991), Regression with frailty in survival analysis. *Biometrics* **47**, 461-66.

Examples

```

data(Kidney)
clayton_cox <- rc_spCox_copula(data = Kidney,
                             var_list = c("age", "sex", "disease"),
                             copula = "Clayton",
                             method = "BFGS",
                             B = 2)
summary(clayton_cox)

```

lines.CopulaCenR *Plotting for CopulaCenR fits*

Description

Plotting for CopulaCenR fits from ic_spTran_copula, rc_spCox_copula, ic_par_copula and rc_par_copula.

Usage

```

## S3 method for class 'CopulaCenR'
lines(
  x,
  y,
  class = "joint",
  newdata,
  evalPoints = 50,
  evalTimes1 = NULL,
  evalTimes2 = NULL,
  plot_margin = 1,
  cond_time = NULL,
  cond_margin = 2,
  plotly_object = NULL,
  ...
)

```

Arguments

x	an object of ic_spTran_copula, rc_spCox_copula, ic_par_copula, rc_par_copula
y	new data frame with colname names id, ind and covariate
class	one of "joint", "conditional" or "marginal"
newdata	new data frame (ignored if y is included)
evalPoints	number of time points to be evaluated; default is 50
evalTimes1	a vector of times for margin 1 to be evaluated; default is NULL; will override evalPoints if non-NULL
evalTimes2	a vector of times for margin 2 to be evaluated

plot_margin	for class = "marginal" only; indicator of which margin to plot (either 1 or 2); default is 1 for margin 1
cond_time	for class = "conditional" only; the time by which event has occurred in the margin indicated by cond_margin; must be smaller than the largest observed time
cond_margin	for class = "conditional" only; indicator of the margin where event has occurred (either 1 or 2); default is 2 for margin 2
plotly_object	only for class = "joint", an object of plot.CopulaCenR
...	further arguments

Details

y must be a data frame with columns id (subject id), ind (1,2 for two margins) and covariates. The argument class determines the plot: "joint" for joint survival probabilities, "conditional" for conditional probabilities and "marginal" for marginal probabilities.

The function evaluates on a series of time points (given by evalPoints or evalTimes; evalTimes will override evalPoints). By default, the time points are automatically selected by specifying the number of points (evalPoints = 50). Users can also provide the specific time points through evalTimes1 and evalTimes2 for the two margins, respectively. When class = "conditional", only evalTimes1 is needed and the evaluation times are actually evalTimes1 plus cond_time.

If class = "conditional", one needs to specify the margin that has the event (by cond_margin) and time when the event has occurred (by cond_time). For example, if cond_margin = 2 and cond_time = 5, then the function produces the conditional survival probability (after time 5) in margin 1 given that margin 2 has got an event by time 5. This measurement is useful for predicting the second event given the first event has occurred. See the example for details.

If class = "marginal", one needs to specify which margin to plot through the argument plot_margin. See the example for details.

If class = "joint", one needs to include a plot_ly object (from plot.CopulaCenR with class = "joint") through the argument plotly_object. See the example for details.

Value

a 3D joint survival distribution plot if class = "joint"; a 2D survival distribution plot if class = "marginal" or "conditional".

Examples

```
data(AREDS)
# fit a Copula2-Sieve model
copula2_sp <- ic_spTran_copula(data = AREDS, copula = "Copula2",
  l = 0, u = 15, m = 3, r = 3,
  var_list = c("ENROLLAGE", "rs2284665", "SevScaleBL"))
newdata = data.frame(id = rep(1:3, each=2), ind = rep(c(1,2),3),
```

```

        SevScaleBL = rep(3,6), ENROLLAGE = rep(60,6),
        rs2284665 = c(0,0,1,1,2,2))
# Plot marginal survival probabilities
plot(x = copula2_sp, class = "marginal",
     newdata = newdata[newdata$id==1,],
     plot_margin = 1, ylim = c(0.6,1),
     ylab = "Marginal Survival Probability")
lines(x = copula2_sp, class = "marginal",
      newdata = newdata[newdata$id==2,],
      plot_margin = 1, lty = 2)
legend("bottomleft", c("id: 1","id: 2"), lty = c(1,2))

# Plot conditional survival probabilities
plot(x = copula2_sp, class = "conditional",
     newdata = newdata[newdata$id==1,],
     cond_margin = 2, cond_time = 5, ylim = c(0.25,1),
     xlab = "years", ylab = "Conditional Survival Probability")
lines(x = copula2_sp, class = "conditional",
      newdata = newdata[newdata$id==2,],
      cond_margin = 2, cond_time = 5, lty = 2)
legend("bottomleft", c("id: 1","id: 2"), lty = c(1,2))

# Plot joint survival probabilities
plot3d <- plot(x = copula2_sp, class = "joint",
              newdata = newdata[newdata$id==1,])
plot3d <- lines(x = copula2_sp, class = "joint",
               newdata = newdata[newdata$id==2,], plotly_object = plot3d)

```

logLik.CopulaCenR *the log-likelihood of a CopulaCenR object*

Description

the log-likelihood of a CopulaCenR object

Usage

```
## S3 method for class 'CopulaCenR'
logLik(object, ...)
```

Arguments

object	a CopulaCenR object
...	further arguments

lrt_copula	<i>Likelihood-ratio test for covariate effect(s) in copula models</i>
------------	---

Description

This function (`lrt_copula`) is used to perform the likelihood ratio test (LRT) between two nested copula models

Usage

```
lrt_copula(model1, model2)
```

Arguments

<code>model1</code>	The output of the larger model
<code>model2</code>	The output of the smaller model

Value

the LRT statistics, p value

Examples

```
#' # Likelihood-ratio test for "rs2284665" in AREDS data
data(AREDS)
# Fit null model without "rs2284665"
copula2_sp_null <- ic_spTran_copula(data = AREDS, copula = "Copula2",
  l = 0, u = 15, m = 3, r = 3,
  var_list = c("SevScaleBL"))
# Fit full model
copula2_sp <- ic_spTran_copula(data = AREDS, copula = "Copula2",
  l = 0, u = 15, m = 3, r = 3,
  var_list = c("rs2284665", "SevScaleBL"))
lrt_copula(model1 = copula2_sp, model2 = copula2_sp_null)
```

<code>plot.CopulaCenR</code>	<i>Plotting for CopulaCenR fits</i>
------------------------------	-------------------------------------

Description

Plotting for CopulaCenR fits from `ic_spTran_copula`, `rc_spCox_copula`, `ic_par_copula` and `rc_par_copula`.

Usage

```
## S3 method for class 'CopulaCenR'
plot(
  x,
  y,
  class = "joint",
  newdata,
  evalPoints = 50,
  evalTimes1 = NULL,
  evalTimes2 = NULL,
  plot_margin = 1,
  cond_time = NULL,
  cond_margin = 2,
  type = "l",
  xlab = "years",
  ylab = "survival probability",
  cex.main = 1.4,
  cex.lab = 1.4,
  cex.axis = 1.4,
  legend = TRUE,
  ...
)
```

Arguments

<code>x</code>	an object of <code>ic_spTran_copula</code> or <code>rc_spCox_copula</code> or <code>ic_par_copula</code> or <code>rc_par_copula</code>
<code>y</code>	new data frame with colname names <code>id</code> , <code>ind</code> and <code>covariate</code>
<code>class</code>	one of "joint", "conditional" or "marginal"
<code>newdata</code>	new data frame (ignored if <code>y</code> is included)
<code>evalPoints</code>	number of time points to be evaluated in both margins; default is 50
<code>evalTimes1</code>	a vector of times for margin 1 to be evaluated; default is NULL; will override <code>evalPoints</code> if non-NULL
<code>evalTimes2</code>	a vector of times for margin 2 to be evaluated
<code>plot_margin</code>	for <code>class = "marginal"</code> only; indicator of which margin to plot (either 1 or 2); default is 1 for margin 1
<code>cond_time</code>	for <code>class = "conditional"</code> only; the time by which event has occurred in the margin indicated by <code>cond_margin</code> ; must be smaller than the largest observed time
<code>cond_margin</code>	for <code>class = "conditional"</code> only; indicator of the margin where event has occurred (either 1 or 2); default is 2 for margin 2
<code>type</code>	type of plot with default type = "l".
<code>xlab</code>	a title for the x axis.
<code>ylab</code>	a title for the x axis.

cex.main	cex for main.
cex.lab	cex for lab.
cex.axis	cex for axis.
legend	whether to show legend with default legend = TRUE.
...	further arguments

Details

y must be a data frame with columns id (subject id), ind (1,2 for two margins) and covariates. The argument class determines the plot: "joint" for joint survival probabilities, "conditional" for conditional probabilities and "marginal" for marginal probabilities.

The function evaluates on a series of time points (given by evalPoints or evalTimes; evalTimes will override evalPoints). By default, the time points are automatically selected by specifying the number of points (evalPoints = 50). Users can also provide the specific time points through evalTimes1 and evalTimes2 for the two margins, respectively. When class = "conditional", only evalTimes1 is needed and the evaluation times are actually evalTimes1 plus cond_time.

If class = "conditional", one needs to specify the margin that has the event (by cond_margin) and time when the event has occurred (by cond_time). For example, if cond_margin = 2 and cond_time = 5, then the function produces the conditional survival probability (after time 5) in margin 1 given that margin 2 has got an event by time 5. This measurement is useful for predicting the second event given the first event has occurred. See the example for details.

If class = "marginal", one needs to specify which margin to plot through the argument plot_margin. See the example for details.

Value

a 3D joint survival distribution plot if class = "joint"; a 2D survival distribution plot if class = "marginal" or "conditional".

Examples

```
data(AREDS)
# fit a Copula2-Sieve model
copula2_sp <- ic_spTran_copula(data = AREDS, copula = "Copula2",
                             l = 0, u = 15, m = 3, r = 3,
                             var_list = c("ENROLLAGE", "rs2284665", "SevScaleBL"))
newdata = data.frame(id = rep(1, each=2), ind = rep(c(1,2),1),
                     SevScaleBL = rep(3,2), ENROLLAGE = rep(60,2),
                     rs2284665 = c(0,0))
# Plot joint survival probabilities
plot(x = copula2_sp, class = "joint", newdata = newdata)

# Plot conditional survival probabilities
plot(x = copula2_sp, class = "conditional", newdata = newdata,
     cond_margin = 2, cond_time = 5, ylim = c(0.25,1),
```

```

      ylab = "Conditional Survival Probability")

# Plot marginal survival probabilities
plot(x = copula2_sp, class = "marginal", newdata = newdata,
      plot_margin = 1, ylim = c(0.6,1),
      ylab = "Marginal Survival Probability")

```

predict.CopulaCenR *Predictions from CopulaCenR regression models*

Description

Predictions for new observations based on `ic_spTran_copula`, `rc_spCox_copula`, `ic_par_copula` and `rc_par_copula`.

Usage

```

## S3 method for class 'CopulaCenR'
predict(object, newdata, type = "lp", ...)

```

Arguments

<code>object</code>	a CopulaCenR object from <code>ic_spTran_copula</code> , <code>rc_spCox_copula</code> , <code>ic_par_copula</code> and <code>rc_par_copula</code>
<code>newdata</code>	a data frame (see details)
<code>type</code>	"lp" for linear predictors or "survival" for marginal and joint survival probabilities
<code>...</code>	further arguments

Details

For the `newdata`, when `type = "survival"`, it must be a data frame with columns `id` (subject id), `ind` (1,2 for two margins), `time` (to be evaluated) and `covariates`; when `type = "lp"`, the `newdata` needs to have `id`, `ind` and `covariates`, but `time` is not needed.

When the argument `type = "lp"`, it gives a linear predictor for each margin (i.e., log hazards ratio in the proportional hazards model, log proportional odds in the proportional odds model).

When the argument `type = "survival"`, the marginal and joint survival values will be evaluated at the given time points in the `newdata`.

Value

If `type = "lp"`, it returns a data frame with `id`, `lp1` (linear predictor for margin 1), `lp2`. If `type = "survival"`, it returns a data frame with `id`, `t1` (evaluated times for the margin 1), `t2`, `S1` (predicted marginal survival probabilities for margin 1), `S2` and `S12` (the predicted joint survival probabilities at `t1`, `t2`)

Examples

```

data(AREDS)
# fit a Copula2-Sieve model
copula2_sp <- ic_spTran_copula(data = AREDS, copula = "Copula2",
                             l = 0, u = 15, m = 3, r = 3,
                             var_list = c("ENROLLAGE", "rs2284665", "SevScaleBL"))
# Predicted probabilities for newdata
newdata = data.frame(id = rep(1:3, each=2), ind = rep(c(1,2),3),
                    time = c(2,3,5,6,7,8),
                    SevScaleBL = rep(3,6),
                    ENROLLAGE = rep(60,6),
                    rs2284665 = c(0,0,1,1,2,2))
output <- predict(object = copula2_sp, newdata = newdata)

```

```

print.CopulaCenR      Printing outputs of a CopulaCenR object

```

Description

Printing outputs of a CopulaCenR object

Usage

```

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

```

Arguments

x	a CopulaCenR object
...	further arguments

```

print.summary.CopulaCenR
      Print the summary of a CopulaCenR object

```

Description

Print the summary of a CopulaCenR object

Usage

```

## S3 method for class 'summary.CopulaCenR'
print(x, ...)

```

Arguments

x	a summary.CopulaCenR object
...	further arguments

rc_par_copula	<i>Copula regression models with parametric margins for bivariate right-censored data</i>
---------------	---

Description

Fits a copula model with parametric margins for bivariate right-censored data.

Usage

```
rc_par_copula(
  data,
  var_list,
  copula = "Clayton",
  m.dist = "Weibull",
  method = "BFGS",
  iter = 500,
  stepsize = 1e-06,
  control = list()
)
```

Arguments

data	a data frame; must have id (subject id), ind (1,2 for two margins), obs_time, status (0 for right-censoring, 1 for event).
var_list	the list of covariates to be fitted into the model.
copula	specify the copula family.
m.dist	specify the marginal baseline distribution.
method	optimization method (see ?optim); default is "BFGS"; also can be "Newton" (see ?nlm).
iter	number of iterations when method = "Newton"; default is 500.
stepsize	size of optimization step when method = "Newton"; default is 1e-6.
control	a list of control parameters for methods other than "Newton"; see ?optim.

Details

The input data must be a data frame with columns id (subject id), ind (1,2 for two margins; each id must have both ind = 1 and 2), obs_time, status (0 for right-censoring, 1 for event) and covariates.

The supported copula models are "Clayton", "Gumbel", "Frank", "AMH", "Joe" and "Copula2". The "Copula2" model is a two-parameter copula model that incorporates Clayton and Gumbel as special cases. The parametric generator functions of copula functions are list below:

The Clayton copula has a generator

$$\phi_{\eta}(t) = (1+t)^{-1/\eta},$$

with $\eta > 0$ and Kendall's $\tau = \eta/(2+\eta)$.

The Gumbel copula has a generator

$$\phi_{\eta}(t) = \exp(-t^{1/\eta}),$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 1/\eta$.

The Frank copula has a generator

$$\phi_{\eta}(t) = -\eta^{-1} \log\{1 + e^{-t}(e^{-\eta} - 1)\},$$

with $\eta \geq 0$ and Kendall's $\tau = 1 + 4\{D_1(\eta) - 1\}/\eta$, in which $D_1(\eta) = \frac{1}{\eta} \int_0^{\eta} \frac{t}{e^t - 1} dt$.

The AMH copula has a generator

$$\phi_{\eta}(t) = (1-\eta)/(e^t - \eta),$$

with $\eta \in [0, 1)$ and Kendall's $\tau = 1 - 2\{(1-\eta)^2 \log(1-\eta) + \eta\}/(3\eta^2)$.

The Joe copula has a generator

$$\phi_{\eta}(t) = 1 - (1 - e^{-t})^{1/\eta},$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 4 \sum_{k=1}^{\infty} \frac{1}{k(\eta k + 2)\{\eta(k-1) + 2\}}$.

The Two-parameter copula (Copula2) has a generator

$$\phi_{\eta}(t) = \{1/(1+t^{\alpha})\}^{\kappa},$$

with $\alpha \in (0, 1]$, $\kappa > 0$ and Kendall's $\tau = 1 - 2\alpha\kappa/(2\kappa + 1)$.

The supported marginal distributions are "Weibull" (proportional hazards), "Gompertz" (proportional hazards) and "Loglogistic" (proportional odds). These marginal distributions are listed below and we also assume the same baseline parameters between two margins.

The Weibull (PH) survival distribution is

$$\exp\{-(t/\lambda)^k e^{Z^T \beta}\},$$

with $\lambda > 0$ as scale and $k > 0$ as shape.

The Gompertz (PH) survival distribution is

$$\exp\{-\frac{b}{a}(e^{at} - 1)e^{Z^T \beta}\},$$

with $a > 0$ as shape and $b > 0$ as rate.

The Loglogistic (PO) survival distribution is

$$\{1 + (t/\lambda)^k e^{Z^T \beta}\}^{-1},$$

with $\lambda > 0$ as scale and $k > 0$ as shape.

Optimization methods can be all methods (except "Brent") from optim, such as "Nelder-Mead", "BFGS", "CG", "L-BFGS-B", "SANN". Users can also use "Newton" (from nlm).

Value

a CopulaCenR object summarizing the model. Can be used as an input to general S3 methods including summary, print, plot, lines, coef, logLik, AIC, BIC, fitted, predict.

Source

Tao Sun, Yi Liu, Richard J. Cook, Wei Chen and Ying Ding (2019). Copula-based Score Test for Bivariate Time-to-event Data, with Application to a Genetic Study of AMD Progression. *Lifetime Data Analysis* 25(3), 546-568.

Tao Sun and Ying Ding (In Press). Copula-based Semiparametric Regression Model for Bivariate Data under General Interval Censoring. *Biostatistics*. DOI: 10.1093/biostatistics/kxz032.

Examples

```
# fit a Clayton-Weibull model
data(DRS)
clayton_wb <- rc_par_copula(data = DRS, var_list = "treat",
                           copula = "Clayton",
                           m.dist = "Weibull")
summary(clayton_wb)
```

rc_scmprisk_Cox

Copula regression models with Cox margins for semi-competing risk data under right censoring cases

Description

Fits a copula model with Cox margins for semi-competing risk data under right censoring cases.

Usage

```
rc_scmprisk_Cox(
  data,
  var_list,
  copula_type = "Clayton",
  l1 = 0,
  l2 = 0,
  m1 = 3,
  m2 = 3,
  u1 = NULL,
  u2 = NULL,
  eta_ini_ini = 2,
  method1a1 = "BFGS",
  method1a2 = "BFGS",
  method1b = "BFGS",
  method2 = "BFGS",
  stepsize = 10000,
```

```

    initial_par1a1 = NULL,
    initial_par1a2 = NULL
  )

```

Arguments

<code>data</code>	a data frame. Each row is a single individual with single observation. Must have <code>time1</code> (time for non-terminal event), <code>time2</code> (time for terminal event), <code>status1</code> (indicator for non-terminal event, 0 if exactly observe, 1 if censored by terminal event, end of cohort or loss to follow-up), <code>status2</code> (indicator for terminal event, 0 if exactly observe, 1 if censored by end of cohort or loss to follow-up), and <code>covariates</code> by column.
<code>var_list</code>	List of covariates to be included in the model.
<code>copula_type</code>	The type of copula to use (e.g., "Clayton", "Gumbel").
<code>l1</code>	Lower bound for Bernstein polynomial for event 1 (default is 0).
<code>l2</code>	Lower bound for Bernstein polynomial for event 2 (default is 0).
<code>m1</code>	Order of Bernstein polynomial for event 1 (default is 3).
<code>m2</code>	Order of Bernstein polynomial for event 2 (default is 3).
<code>u1</code>	Upper bound for Bernstein polynomial for event 1 (default is $\max(\text{obs_time}) + 1$).
<code>u2</code>	Upper bound for Bernstein polynomial for event 2 (default is $\max(\text{obs_time}) + 1$).
<code>eta_ini_ini</code>	a vector of initial values for copula parameters, default is 2
<code>method1a1</code>	Optimization method for step 1a1 (default is "BFGS").
<code>method1a2</code>	Optimization method for step 1a2 (default is "BFGS").
<code>method1b</code>	Optimization method for step 1b (default is "BFGS").
<code>method2</code>	Optimization method for step 2 (default is "BFGS").
<code>stepsize</code>	Maximum number of iterations for optimization steps (default is 10000).
<code>initial_par1a1</code>	initial value for parameter when estimating in step 1a_1.
<code>initial_par1a2</code>	initial value for parameter when estimating in step 1a_2.

Details

The input data must be a data frame. Each row is a single individual with single observation. Must have `time1` (time for non-terminal event), `time2` (time for terminal event), `status1` (indicator for non-terminal event, 0 if exactly observe, 1 if censored by terminal event, end of cohort or loss to follow-up), `status2` (indicator for terminal event, 0 if exactly observe, 1 if censored by end of cohort or loss to follow-up), and `covariates` by column.

The supported copula model in this version is "Clayton" and "Gumbel". The parametric generator functions of copula functions are list below:

The Clayton copula has a generator

$$\phi_{\eta}(t) = (1 + t)^{-1/\eta},$$

with $\eta > 0$ and Kendall's $\tau = \eta/(2 + \eta)$.

The Gumbel copula has a generator

$$\phi_{\eta}(t) = \exp(-t^{1/\eta}),$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 1/\eta$.

The marginal Cox semiparametric models are built based on Bernstein polynomials, which is formulated below:

$$S(t|Z) = \exp[-\Lambda(t)e^{Z^T\beta}],$$

where t is time, Z is covariate, β is the coefficient vector, and $\Lambda(t)$ is the cumulative baseline hazard function. We approximate $\Lambda(t)$ in a sieve space constructed by Bernstein polynomials with degree m . By default, $m = 3$. In the end, all model parameters are estimated by the sieve estimators (Sun and Ding, In Press).

The Cox proportional hazards model assumes that the hazard ratio is constant over time, with the form $h(t|Z) = h_0(t)e^{Z^T\beta}$, where $h_0(t)$ is the baseline hazard function and Z is the covariate vector. This formulation is flexible and allows $\Lambda(t)$ to be approximated using Bernstein polynomials, which can be tuned by the degree parameter m . The degree of Bernstein polynomial m can be selected based on the AIC value to provide an optimal balance between model complexity and fit.

Optimization methods can be all methods (except "Brent") from `optim`, such as "Nelder-Mead", "BFGS", "CG", "L-BFGS-B", "SANN".

Value

a `CopulaCenR` object summarizing the model. Can be used as an input to general S3 methods including `summary`, `print`, `coef`, `logLik`, `AIC`.

Source

Tao Sun, Yunlong Li, Zhengyan Xiao, Ying Ding, Xiaojun Wang (2022). Semiparametric copula method for semi-competing risks data subject to interval censoring and left truncation: Application to disability in elderly. *Statistical Methods in Medical Research* (Accepted).

Tao Sun, Weijie Liang, Gongzi Zhang, Danhui Yi, Ying Ding, Lihai Zhang (2024). Penalised semi-parametric copula method for semi-competing risks data: Application to hip fracture in elderly. *Journal of the Royal Statistical Society Series C: Applied Statistics* (Accepted)

Examples

```
# fit a rc_Clayton_Cox model
data("data_scmprisk_rc")
Clayton_rc <- rc_scmprisk_Cox(data_scmprisk_rc, var_list = c("x1", "x2", "x3"), copula = "Clayton",
  l1=0, m1 = 3,
  l2=0, m2 = 3, eta_ini_ini = 2, method1a1="Nelder-Mead", method1a2="Nelder-Mead"
)
Clayton_rc
```

 rc_scmprisk_sp_copula_pen

Penalized copula regression models with Cox semiparametric margins for semi-competing risk data under right-censoring.

Description

Fits a penalized copula model with Cox semiparametric margins for semi-competing risk data under right-censoring.

Usage

```
rc_scmprisk_sp_copula_pen(
  data,
  var_list1,
  var_list2,
  m1,
  m2,
  initial,
  a,
  b,
  pen1,
  pen2,
  copula
)
```

Arguments

data	a data frame; must have id (subject id), ind (1,2 for two margins), obs_time, status (0 for right-censoring, 1 for event).
var_list1	the list of covariates to be fitted into the copula model for non-terminal event.
var_list2	the list of covariates to be fitted into the copula model for terminal event.
m1	integer, degree of Bernstein polynomials for non-terminal event; default is 3.
m2	integer, degree of Bernstein polynomials for terminal event; default is 3.
initial	a vector of initial values for all parameters, including phi1 and phi2 (two Bernstein polynomials parameters), beta1 and beta2 (regression coefficients in Cox margins), eta (copula parameters).
a	Tuning parameters in penalty function for non-terminal event.
b	Tuning parameters in penalty function for terminal event.
pen1	Types of penalty function for non-terminal event, including "NOPEN", "RIDGE", "BAR", "LASSO", "MCP", "SCAD".
pen2	Types of penalty function for terminal event, including "NOPEN", "RIDGE", "BAR", "LASSO", "MCP", "SCAD".
copula	Types of copula, including "Clayton", "Gumbel".

Value

parameter estimates and BIC

Source

Tao Sun, Weijie Liang, Gongzi Zhang, Danhui Yi, Ying Ding, Lihai Zhang (2023+). Penalized semiparametric copula method for semi-competing risks data: Application to hip fracture in elderly. JRSSC.

Examples

```
## Not run:
data("data_sim_scmprisk_vs")
var_list = paste0('x',seq(1,5,1))
phi1_ini = c(0,0,0,0)
phi2_ini = c(0,0,0,0)
beta1_ini = c(0,0,0,0,0)
beta2_ini = c(0,0,0,0,0)
eta_ini = 1
initial = c(phi1_ini,phi2_ini,beta1_ini, beta2_ini, eta_ini)
# obtain initial parameter estimates by ridge penalty
fit0 = rc_scmprisk_sp_copula_pen(data=data_sim_scmprisk_vs,
                               var_list1 = var_list, var_list2 = var_list,
                               m1=3, m2=3, initial=initial,
                               a=0.1, b=0.1, pen1='RIDGE', pen2='RIDGE',
                               copula='Clayton')
est_ini = c(fit0$Est_phi1,fit0$Est_phi2,fit0$Est_beta1,fit0$Est_beta2,fit0$Est_eta)

fit = rc_scmprisk_sp_copula_pen(data=data_sim_scmprisk_vs,
                               var_list1 = var_list, var_list2 = var_list,
                               m1=3, m2=3, initial=est_ini,
                               a=0.2, b=0.2, pen1='MCP', pen2='MCP',
                               copula='Clayton')

fit$Est_beta1
fit$Est_beta2

## End(Not run)
```

rc_spCox_copula

Copula regression models with Cox semiparametric margins for bivariate right-censored data

Description

Fits a copula model with Cox semiparametric margins for bivariate right-censored data.

Usage

```
rc_spCox_copula(
  data,
  var_list,
  copula = "Clayton",
  method = "BFGS",
  iter = 500,
  stepsize = 1e-06,
  control = list(),
  B = 100,
  seed = 1
)
```

Arguments

<code>data</code>	a data frame; must have <code>id</code> (subject id), <code>ind</code> (1,2 for two margins), <code>obs_time</code> , <code>status</code> (0 for right-censoring, 1 for event).
<code>var_list</code>	the list of covariates to be fitted into the model.
<code>copula</code>	specify the copula family.
<code>method</code>	optimization method (see <code>?optim</code>); default is "BFGS"; also can be "Newton" (see <code>?nlm</code>).
<code>iter</code>	number of iterations when <code>method = "Newton"</code> ; default is 500.
<code>stepsize</code>	size of optimization step when <code>method = "Newton"</code> ; default is 1e-6.
<code>control</code>	a list of control parameters for methods other than "Newton"; see <code>?optim</code> .
<code>B</code>	number of bootstraps for estimating standard errors with default 100;
<code>seed</code>	the bootstrap seed; default is 1

Details

The input data must be a data frame with columns `id` (subject id), `ind` (1,2 for two margins; each id must have both `ind = 1` and `2`), `obs_time`, `status` (0 for right-censoring, 1 for event) and covariates.

The supported copula models are "Clayton", "Gumbel", "Frank", "AMH", "Joe" and "Copula2". The "Copula2" model is a two-parameter copula model that incorporates Clayton and Gumbel as special cases. The parametric generator functions of copula functions are list below:

The Clayton copula has a generator

$$\phi_{\eta}(t) = (1 + t)^{-1/\eta},$$

with $\eta > 0$ and Kendall's $\tau = \eta/(2 + \eta)$.

The Gumbel copula has a generator

$$\phi_{\eta}(t) = \exp(-t^{1/\eta}),$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 1/\eta$.

The Frank copula has a generator

$$\phi_{\eta}(t) = -\eta^{-1} \log\{1 + e^{-t}(e^{-\eta} - 1)\},$$

with $\eta \geq 0$ and Kendall's $\tau = 1 + 4\{D_1(\eta) - 1\}/\eta$, in which $D_1(\eta) = \frac{1}{\eta} \int_0^{\eta} \frac{t}{e^t - 1} dt$.

The AMH copula has a generator

$$\phi_{\eta}(t) = (1 - \eta)/(e^t - \eta),$$

with $\eta \in [0, 1)$ and Kendall's $\tau = 1 - 2\{(1 - \eta)^2 \log(1 - \eta) + \eta\}/(3\eta^2)$.

The Joe copula has a generator

$$\phi_{\eta}(t) = 1 - (1 - e^{-t})^{1/\eta},$$

with $\eta \geq 1$ and Kendall's $\tau = 1 - 4 \sum_{k=1}^{\infty} \frac{1}{k(\eta k + 2)\{\eta(k-1) + 2\}}$.

The Two-parameter copula (Copula2) has a generator

$$\phi_{\eta}(t) = \{1/(1 + t^{\alpha})\}^{\kappa},$$

with $\alpha \in (0, 1]$, $\kappa > 0$ and Kendall's $\tau = 1 - 2\alpha\kappa/(2\kappa + 1)$.

The marginal distribution is a Cox semiparametric proportional hazards model. The copula parameter and coefficient standard errors are estimated from bootstrap.

Optimization methods can be all methods (except "Brent") from `optim`, such as "Nelder-Mead", "BFGS", "CG", "L-BFGS-B", "SANN". Users can also use "Newton" (from `nlm`).

Value

a `CopulaCenR` object summarizing the model. Can be used as an input to general S3 methods including `summary`, `print`, `plot`, `lines`, `coef`, `logLik`, `AIC`, `BIC`, `fitted`, `predict`.

Source

Tao Sun, Yi Liu, Richard J. Cook, Wei Chen and Ying Ding (2019). Copula-based Score Test for Bivariate Time-to-event Data, with Application to a Genetic Study of AMD Progression. *Lifetime Data Analysis* 25(3), 546-568.

Tao Sun and Ying Ding (In Press). Copula-based Semiparametric Regression Model for Bivariate Data under General Interval Censoring. *Biostatistics*. DOI: 10.1093/biostatistics/kxz032.

Examples

```
# fit a Clayton-Cox model
data(DRS)
clayton_cox <- rc_spCox_copula(data = DRS, var_list = "treat",
                             copula = "Clayton", B = 2)
summary(clayton_cox)
```

score_copula	<i>Generalized score test for covariate effect(s)</i>
--------------	---

Description

Generalized score test on covariate effect(s) under a fitted copula model.

Usage

```
score_copula(object, var_score)
```

Arguments

object	The output object from the main functions (rc_par_copula, rc_spCox_copula, ic_spTran_copula, ic_par_copula) under the null hypothesis
var_score	the list of covariates to be tested by the score test

Value

the score statistics, p value

Examples

```
# Score test for "rs2284665" in AREDS data
# fit a Copula2-semiparametric model under NULL
data(AREDS)
copula2_sp_null <- ic_spTran_copula(data = AREDS, copula = "Copula2",
  l = 0, u = 15, m = 3, r = 3,
  var_list = c("ENROLLAGE", "SevScaleBL"))
score_copula(object = copula2_sp_null, var_score = "rs2284665")
```

summary.CopulaCenR	<i>Summarizing outputs of a CopulaCenR object</i>
--------------------	---

Description

Summarizing outputs of a CopulaCenR object

Usage

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

Arguments

object	a CopulaCenR object
...	further arguments

tau_copula

Calculate Kendall's tau

Description

To obtain Kendall's tau from copula parameter(s)

Usage

```
tau_copula(eta, copula)
```

Arguments

eta copula parameter(s); if copula = "Copula2", input α and κ
 copula specify the type of copula model

Details

The supported copula models are "Clayton", "Gumbel", "Frank", "AMH", "Joe" and "Copula2". The "Copula2" model is a two-parameter copula model that incorporates Clayton and Gumbel as special cases.

The Kendall's τ formulas are list below:

The Clayton copula Kendall's $\tau = \eta/(2 + \eta)$.

The Gumbel copula Kendall's $\tau = 1 - 1/\eta$.

The Frank copula Kendall's $\tau = 1 + 4\{D_1(\eta) - 1\}/\eta$, in which $D_1(\eta) = \frac{1}{\eta} \int_0^\eta \frac{t}{e^t - 1} dt$.

The AMH copula Kendall's $\tau = 1 - 2\{(1 - \eta)^2 \log(1 - \eta) + \eta\}/(3\eta^2)$.

The Joe copula Kendall's $\tau = 1 - 4 \sum_{k=1}^{\infty} \frac{1}{k(\eta k + 2)\{\eta(k-1) + 2\}}$.

The Two-parameter copula (Copula2) Kendall's $\tau = 1 - 2\alpha\kappa/(2\kappa + 1)$.

Value

Kendall's τ

Source

Ali MM, Mikhail NN, Haq MS (1978). A Class of Bivariate Distributions Including the Bi-variate Logistic. *Journal of Multivariate Analysis* doi:10.1016/0047-259X(78)90063-5.

Clayton DG (1978). A Model for Association in Bivariate Life Tables and Application in Epidemiological Studies of Familial Tendency in Chronic Disease Incidence. *Biometrika* doi:10.2307/2335289.

Gumbel EJ (1960). Bivariate Exponential Distributions. *Journal of the American Statistical Association* doi:10.2307/2281591.

Joe H (1993). Parametric Families of Multivariate Distributions with Given Margins. *Journal of Multivariate Analysis* doi:10.1006/jmva.1993.1061.

Joe H (1997). Multivariate Models and Dependence Concepts. *Chapman & Hall, London*.
Frank MJ (1979). On the Simultaneous Associativity of $F(x, y)$ and $x + y - F(x, y)$. *Aequationes Mathematicae*.

Examples

```
# fit a Copula2-Semiparametric model
data(AREDS)
copula2_sp <- ic_spTran_copula(data = AREDS, copula = "Copula2",
                             l = 0, u = 15, m = 3, r = 3,
                             var_list = c("ENROLLAGE", "rs2284665", "SevScaleBL"))
tau_copula(eta = as.numeric(coef(copula2_sp)[c("alpha", "kappa")]),
           copula = "Copula2")
```

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