Package ‘survPen’

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Title Multidimensional Penalized Splines for Survival and Net Survival Models

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Description
Fits hazard and excess hazard models with multidimensional penalized splines allowing for time-dependent effects, non-linear effects and interactions between several continuous covariates. In survival and net survival analysis, in addition to modelling the effect of time (via the baseline hazard), one has often to deal with several continuous covariates and model their functional forms, their time-dependent effects, and their interactions. Model specification becomes therefore a complex problem and penalized regression splines represent an appealing solution to that problem as splines offer the required flexibility while penalization limits overfitting issues. Current implementations of penalized survival models can be slow or unstable and sometimes lack some key features like taking into account expected mortality to provide net survival and excess hazard estimates. In contrast, survPen provides an automated, fast, and stable implementation (thanks to explicit calculation of the derivatives of the likelihood) and offers a unified framework for multidimensional penalized hazard and excess hazard models. survPen may be of interest to those who 1) analyse any kind of time-to-event data: mortality, disease relapse, machinery breakdown, unemployment, etc 2) wish to describe the associated hazard and to understand which predictors impact its dynamics.


Depends R (>= 3.4.0)

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Imports statmod, stats, Rcpp (>= 1.0.2)

LinkingTo Rcpp, RcppEigen

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Description

colSums of a matrix

Usage

colSums2(Mat)

Arguments

Mat a matrix.

Value

colSums(Mat)

Description

Sum-to-zero constraint

Usage

constraint(X, S, Z = NULL)

Arguments

X A design matrix
S A penalty matrix or a list of penalty matrices
Z A list of sum-to-zero constraint matrices; default is NULL

Value

List of objects with the following items:

X Design matrix
S Penalty matrix or list of penalty matrices
Z List of sum-to-zero constraint matrices
Examples

library(survPen)
set.seed(15)
X <- matrix(rnorm(10*3), nrow=10, ncol=3)
S <- matrix(rnorm(3*3), nrow=3, ncol=3) ; S <- 0.5*(S + t(S))

# applying sum-to-zero constraint to a design matrix and a penalty matrix
constr <- constraint(X,S)

cor.var

Implementation of the corrected variance $V_c$

Description
Takes the model at convergence and calculates the variance matrix corrected for smoothing parameter uncertainty

Usage
cor.var(model)

Arguments
model survPen object, see survPen.fit for details

Value
survPen object with corrected variance $V_c$

crs
Bases for cubic regression splines (equivalent to "cr" in mgcv)

Description
Builds the design matrix and the penalty matrix for cubic regression splines.

Usage
crs(x, knots = NULL, df = 10, intercept = TRUE)
Arguments

- **x**: Numeric vector
- **knots**: Numeric vectors that specifies the knots of the splines (including boundaries); default is NULL
- **df**: numeric value that indicates the number of knots desired (or degrees of freedom) if knots=NULL; default is 10
- **intercept**: if FALSE, the intercept is excluded from the basis; default is TRUE

Details

See package mgcv and section 4.1.2 of Wood (2006) for more details about this basis

Value

List of three elements

- **bs**: design matrix
- **pen**: penalty matrix
- **knots**: vector of knots (specified or calculated from df)

References


Examples

```r
x <- seq(1,10,length=100)
# natural cubic spline with 3 knots
crs(x,knots=c(1,5,10))
```

---

**crs.FP**

*Penalty matrix constructor for cubic regression splines*

Description

constructs the penalty matrix associated with cubic regression splines basis. This function is called inside **crs**.

Usage

```r
crs.FP(knots, h)
```
**Arguments**

- **knots**: Numeric vectors that specifies the knots of the splines (including boundaries)
- **h**: vector of knots differences (corresponds to `diff(sort(knots))`)

**Value**

List of two elements:

- **F.mat**: matrix used in function `crs` for basis construction
- **P.mat**: penalty matrix

**Examples**

```r
library(survPen)

# construction of the penalty matrix using a sequence of knots
knots <- c(0, 0.25, 0.5, 0.75, 1)
diff.knots <- diff(knots)
crs.FP(knots, diff.knots)
```

**datCancer**

*Patients diagnosed with cervical cancer*

**Description**

A simulated dataset containing the follow-up times of 2000 patients diagnosed with cervical cancer between 1990 and 2010. End of follow-up is June 30th 2013. The variables are as follows:

- **begin**: beginning of follow-up. For illustration purposes about left truncation only (0–1)
- **fu**: follow-up time in years (0–5)
- **age**: age at diagnosis in years, from 21.39 to 99.33
- **yod**: decimal year of diagnosis, from 1990.023 to 2010.999
- **dead**: censoring indicator (1 for dead, 0 for censored)
- **rate**: expected mortality rate (from overall mortality of the general population) (0–0.38)

**Usage**

```r
data(datCancer)
```

**Format**

A data frame with 2000 rows and 6 variables
deriv_R

Derivative of a Choleski factor

Description

Derivative of a Choleski factor

Usage

```r
deriv_R(deriv_Vp, p, R1)
```

Arguments

- `deriv_Vp`: derivatives of the Bayesian covariance matrix wrt rho (log smoothing parameters).
- `p`: number of regression parameters
- `R1`: Choleski factor of Vp

Value

- a list containing the derivatives of R1 wrt rho (log smoothing parameters)

design.matrix

Design matrix for the model needed in Gauss-Legendre quadrature

Description

Builds the design matrix for the whole model when the sum-to-zero constraints are specified. The function is called inside `model.cons` for Gauss-Legendre quadrature.

Usage

```r
design.matrix(
  formula,
  data.spec,
  Z.smf,
  Z.tensor,
  Z.tint,
  list.smf,
  list.tensor,
  list.tint,
  list.rd
)
```
Arguments

- **formula**: formula object identifying the model
- **data.spec**: data frame that represents the environment from which the covariate values and knots are to be calculated
- **Z.smf**: List of matrices that represents the sum-to-zero constraint to apply for `smf` splines
- **Z.tensor**: List of matrices that represents the sum-to-zero constraint to apply for `tensor` splines
- **Z.tint**: List of matrices that represents the sum-to-zero constraint to apply for `tint` splines
- **list.smf**: List of all `smf.smooth.spec` objects contained in the model
- **list.tensor**: List of all `tensor.smooth.spec` objects contained in the model
- **list.tint**: List of all `tint.smooth.spec` objects contained in the model
- **list.rd**: List of all `rd.smooth.spec` objects contained in the model

Value

design matrix for the model

Examples

```r
library(survPen)

# standard spline of time with 4 knots
data <- data.frame(time=seq(0,5,length=100),event=1,t0=0)
form <- ~ smf(time,knots=c(0,1,3,5))
t1 <- eval(substitute(time), data)
t0 <- eval(substitute(t0), data)
event <- eval(substitute(event), data)

# Setting up the model
model.c <- model.cons(form,lambda=0,data.spec=data,t1=t1,t1.name="time",
t0=rep(0,100),t0.name="t0",event=event,event.name="event",
expected=NULL,expected.name=NULL,type="overall",n.legendre=20,
c1="survPen(form,data,t1=time,event=event)",beta.ini=NULL)

# Retrieving the sum-to-zero constraint matrices and the list of knots
Z.smf <- model.c$Z.smf ; list.smf <- model.c$list.smf

# Calculating the design matrix
design.M <- design.matrix(form,data.spec=data,Z.smf=Z.smf,list.smf=list.smf,
Z.tensor=NULL,Z.tint=NULL,list.tensor=NULL,list.tint=NULL,list.rd=NULL)
```
**grad_rho**

**Description**

Gradient vector of LCV and LAML wrt rho (log smoothing parameters)

**Usage**

```r
grad_rho(
  X_GL,
  GL_temp,
  haz_GL,
  deriv_rho_beta,
  weights,
  tm,
  nb_smooth,
  p,
  n_legendre,
  S_list,
  temp_LAML,
  Vp,
  S_beta,
  beta,
  inverse_new_S,
  X,
  temp_deriv3,
  event,
  expected,
  type,
  Ve,
  mat_temp,
  method
)
```

**Arguments**

- **X_GL**: list of matrices (length(X.GL)=n.legendre) for Gauss-Legendre quadrature
- **GL_temp**: list of vectors used to make intermediate calculations and save computation time
- **haz_GL**: list of all the matrix-vector multiplications X.GL[[i]]%*%beta for Gauss Legendre integration in order to save computation time
- **deriv_rho_beta**: first derivative of beta wrt rho (implicit differentiation)
- **weights**: vector of weights for Gauss-Legendre integration on [-1;1]
- **tm**: vector of midpoints times for Gauss-Legendre integration; tm = 0.5*(t1 - t0)
Hess_rho

nb_smooth  number of smoothing parameters
p  number of regression parameters
n_legendre  number of nodes for Gauss-Legendre quadrature
S_list  List of all the rescaled penalty matrices multiplied by their associated smoothing parameters
temp_LAML  temporary matrix used when method="LAML" to save computation time
Vp  Bayesian covariance matrix
S_beta  List such that S_beta[i]=S_list[i]*beta
beta  vector of estimated regression parameters
inverse_new_S  inverse of the penalty matrix
X  design matrix for the model
temp_deriv3  temporary matrix for third derivatives calculation when type="net" to save computation time
event  vector of right-censoring indicators
expected  vector of expected hazard rates
type  "net" or "overall"
Ve  frequentist covariance matrix
mat_temp  temporary matrix used when method="LCV" to save computation time
method  criterion used to select the smoothing parameters. Should be "LAML" or "LCV"; default is "LAML"

Value

List of objects with the following items:

grad_rho  gradient vector of LCV or LAML
deriv_rho_inv_Hess_beta  List of first derivatives of Vp wrt rho
deriv_rho_Hess_unpen_beta  List of first derivatives of the Hessian of the unpenalized log-likelihood wrt rho

Hess_rho  Hessian matrix of LCV and LAML wrt rho (log smoothing parameters)

Description

Hessian matrix of LCV and LAML wrt rho (log smoothing parameters)
Usage

Hess_rho(
    X_GL,  
    X_GL_Q, 
    GL_temp, 
    haz_GL, 
    deriv2_rho_beta, 
    deriv_rho_beta, 
    weights, 
    tm, 
    nb_smooth, 
    p, 
    n_legendre, 
    deriv_rho_inv_Hess_beta, 
    deriv_rho_Hess_unpen_beta, 
    S_list, 
    minus_eigen_inv_Hess_beta, 
    temp_LAML, 
    temp_LAML2, 
    Vp, 
    S_beta, 
    beta, 
    inverse_new_S, 
    X, 
    X_Q, 
    temp_deriv3, 
    temp_deriv4, 
    event, 
    expected, 
    type, 
    Ve, 
    deriv_rho_Ve, 
    mat_temp, 
    deriv_mat_temp, 
    eigen_mat_temp, 
    method)

Arguments

X_GL  
    list of matrices (length(X.GL)=n.legendre) for Gauss-Legendre quadrature

X_GL_Q  
    list of transformed matrices from X_GL in order to calculate only the diagonal of the fourth derivative of the likelihood

GL_temp  
    list of vectors used to make intermediate calculations and save computation time

haz_GL  
    list of all the matrix-vector multiplications X,GL[[i]]%*%beta for Gauss Legendre integration in order to save computation time

deriv2_rho_beta  
    second derivatives of beta wrt rho (implicit differentiation)
Hess_rho

deriv_rho_beta  first derivatives of beta wrt rho (implicit differentiation)
weights  vector of weights for Gauss-Legendre integration on [-1;1]
tm  vector of midpoints times for Gauss-Legendre integration; \( tm = 0.5*(t1 - t0) \)

nb_smooth  number of smoothing parameters
p  number of regression parameters
n_legendre  number of nodes for Gauss-Legendre quadrature

deriv_rho_inv_Hess_beta  list of first derivatives of Vp wrt rho
deriv_rho_Hess_unpen_beta  list of first derivatives of Hessian of unpenalized log likelihood wrt rho
S_list  List of all the rescaled penalty matrices multiplied by their associated smoothing parameters

minus_eigen_inv_Hess_beta  vector of eigenvalues of Vp
temp_LAML  temporary matrix used when method="LAML" to save computation time
temp_LAML2  temporary matrix used when method="LAML" to save computation time
Vp  Bayesian covariance matrix
S_beta  List such that \( S_{beta}[i]=S_{list}[i]%*%beta \)

beta  vector of estimated regression parameters
inverse_new_S  inverse of the penalty matrix
X  design matrix for the model

X_Q  transformed design matrix in order to calculate only the diagonal of the fourth derivative of the likelihood
temp_deriv3  temporary matrix for third derivatives calculation when type="net" to save computation time
temp_deriv4  temporary matrix for fourth derivatives calculation when type="net" to save computation time

event  vector of right-censoring indicators
expected  vector of expected hazard rates

"net" or "overall"
Ve  frequentist covariance matrix
deriv_rho_Ve  list of derivatives of Ve wrt rho
mat_temp  temporary matrix used when method="LCV" to save computation time
deriv_mat_temp  list of derivatives of mat_temp wrt rho
eigen_mat_temp  vector of eigenvalues of mat_temp

method  criterion used to select the smoothing parameters. Should be "LAML" or "LCV"; default is "LAML"

Value

Hessian matrix of LCV or LAML wrt rho
**instr**

*Position of the nth occurrence of a string in another one*

**Description**

Returns the position of the nth occurrence of str2 in str1. Returns 0 if str2 is not found.

**Usage**

\[
\text{instr(str1, str2, startpos = 1, n = 1)}
\]

**Arguments**

- **str1**: main string in which str2 is to be found
- **str2**: substring contained in str1
- **startpos**: starting position in str1; default is 1
- **n**: which occurrence is to be found; default is 1

**Value**

number representing the nth position of str2 in str1

**Examples**

```r
library(survPen)

instr("character test to find the position of the third letter r", "r", n=3)
```

---

**inv.repam**

*Reverses the initial reparameterization for stable evaluation of the log determinant of the penalty matrix*

**Description**

Transforms the final model by reversing the initial reparameterization performed by **repam**. Derives the corrected version of the Bayesian covariance matrix.

**Usage**

\[
\text{inv.repam(model, X.ini, S.pen.ini)}
\]
Arguments

- **model**: survPen object, see `survPen.fit` for details
- **X.ini**: initial design matrix (before reparameterization)
- **S.pen.ini**: initial penalty matrices

Value

survPen object with standard parameterization

Description

Sets up the model before optimization. Builds the design matrix, the penalty matrix and all the design matrices needed for Gauss-Legendre quadrature.

Usage

```r
model.cons(
    formula,
    lambda,
    data.spec,
    t1,
    t1.name,
    t0,
    t0.name,
    event,
    event.name,
    expected,
    expected.name,
    type,
    n.legendre,
    cl,
    beta.ini
)
```

Arguments

- **formula**: formula object identifying the model
- **lambda**: vector of smoothing parameters
- **data.spec**: data frame that represents the environment from which the covariate values and knots are to be calculated
- **t1**: vector of follow-up times
- **t1.name**: name of t1 in data.spec
**Value**

List of objects with the following items:

- **cl**: original `survPen` call
- **type**: "net" or "overall"
- **n.legendre**: number of nodes for Gauss-Legendre quadrature
- **n**: number of individuals
- **p**: number of parameters
- **X.para**: design matrix associated with fully parametric parameters (unpenalized)
- **X.smooth**: design matrix associated with the penalized parameters
- **X**: design matrix for the model
- **leg**: list of nodes and weights for Gauss-Legendre integration on [-1;1] as returned by `gauss.quad`
- **X.GL**: list of matrices (length(X.GL)=n.legendre) for Gauss-Legendre quadrature
- **S**: penalty matrix for the model. Sum of the elements of S.list
- **S.scale**: vector of rescaling factors for the penalty matrices
- **rank.S**: rank of the penalty matrix
- **S.F**: balanced penalty matrix as described in section 3.1.2 of (Wood,2016). Sum of the elements of S.F.list
- **U.F**: Eigen vectors of S.F, useful for the initial reparameterization to separate penalized ad unpenalized subvectors. Allows stable evaluation of the log determinant of S and its derivatives
- **S.smf**: List of penalty matrices associated with all "smf" calls
- **S.tensor**: List of penalty matrices associated with all "tensor" calls
- **S.tint**: List of penalty matrices associated with all "tint" calls
- **S.rd**: List of penalty matrices associated with all "rd" calls
- **smooth.name.smf**: List of names for the "smf" calls associated with S.smf
smooth.name.tensor
List of names for the "tensor" calls associated with S.tensor

smooth.name.tint
List of names for the "tint" calls associated with S.tint

smooth.name.rd
List of names for the "rd" calls associated with S.rd

S.pen
List of all the rescaled penalty matrices redimensioned to df.tot size. Every
element of pen noted \( \text{pen}[i] \) is made from a penalty matrix returned by
smooth.cons and is multiplied by the factor \( S.\text{scale} = \| X \|_I^2 / \| \text{pen}[i] \|_I \)

S.list
Equivalent to S.pen but with every element multiplied by its associated smoothing parameter

S.F.list
Equivalent to S.pen but with every element divided by its Frobenius norm

lambda
vector of smoothing parameters

df.para
degrees of freedom associated with fully parametric terms (unpenalized)

df.smooth
degrees of freedom associated with penalized terms

df.tot
df.para + df.smooth

list.smf
List of all smf.smooth.spec objects contained in the model

list.tensor
List of all tensor.smooth.spec objects contained in the model

list.tint
List of all tint.smooth.spec objects contained in the model

nb.smooth
number of smoothing parameters

Z.smf
List of matrices that represents the sum-to-zero constraints to apply for smf splines

Z.tensor
List of matrices that represents the sum-to-zero constraints to apply for tensor splines

Z.tint
List of matrices that represents the sum-to-zero constraints to apply for tint splines

beta.ini
initial set of regression parameters

Examples

library(survPen)

# standard spline of time with 4 knots

data <- data.frame(time=seq(0,5,length=100),event=1,t0=0)

form <- ~ smf(time,knots=c(0,1,3,5))

t1 <- eval(substitute(time), data)
t0 <- eval(substitute(t0), data)
event <- eval(substitute(event), data)

# The following code sets up everything we need in order to fit the model
model.c <- model.cons(form,lambda=0,data.spec=data,t1=t1,t1.name="time",
t0=rep(0,100),t0.name="t0",event=event,event.name="event",
NR.beta

expected=NULL, expected.name=NULL, type="overall", n.legendre=20,
cl="survPen(form, data, t1=time, event=event)", beta.ini=NULL)

NR.beta  

Inner Newton-Raphson algorithm for regression parameters estimation

Description

Applies Newton-Raphson algorithm for beta estimation. Two specific modifications aim at guaranteeing convergence: first the hessian is perturbed whenever it is not positive definite and second, at each step, if the penalized log-likelihood is not maximized, the step is halved until it is.

Usage

NR.beta(build, beta.ini, detail.beta, max.it.beta = 200, tol.beta = 1e-04)

Arguments

build  list of objects returned by model.cons
beta.ini  vector of initial regression parameters; default is NULL, in which case the first beta will be log(sum(event)/sum(t1)) and the others will be zero (except if there are "by" variables in which case all betas are set to zero)
detail.beta  if TRUE, details concerning the optimization process in the regression parameters are displayed; default is FALSE
max.it.beta  maximum number of iterations to reach convergence in the regression parameters; default is 200
tol.beta  convergence tolerance for regression parameters; default is 1e-04

Details

If we note ll.pen and beta respectively the current penalized log-likelihood and estimated parameters and ll.pen.old and beta.old the previous ones, the algorithm goes on while (abs(ll.pen-ll.pen.old)>tol.beta) or any(abs((beta-beta.old)/beta.old)>tol.beta)

Value

List of objects:

beta  estimated regression parameters
ll.unpen  log-likelihood at convergence
ll.pen  penalized log-likelihood at convergence
haz.GL list of all the matrix-vector multiplications X.GL[ij]*beta for Gauss Legendre integration. Useful to avoid repeating operations in survPen.fit
iter.beta  number of iterations needed to converge
Examples

```r
library(survPen)

# standard spline of time with 4 knots
data <- data.frame(time=seq(0,5,length=100),event=1,t0=0)
form <- ~ smf(time,knots=c(0,1,3,5))
t1 <- eval(substitute(time), data)
t0 <- eval(substitute(t0), data)
event <- eval(substitute(event), data)

# Setting up the model before fitting
model.c <- model.cons(form,lambda=0,data.spec=data,t1=t1,t0.name="time",
t0=rep(0,100),t0.name="t0",event=event,event.name="event",
expected=NULL,expected.name=NULL,type="overall",n.legendre=20,
cl="survPen(form,data,t1=time,event=event)",beta.ini=NULL)

# Estimating the regression parameters at given smoothing parameter (here lambda=0)
Newton1 <- NR.beta(model.c,beta.ini=rep(0,4),detail.beta=TRUE)
```

---

**NR.rho**

*Outer Newton-Raphson algorithm for smoothing parameters estimation via LCV or LAML optimization*

**Description**

Applies Newton-Raphson algorithm for smoothing parameters estimation. Two specific modifications aims at guaranteeing convergence: first the hessian is perturbed whenever it is not positive definite and second, at each step, if LCV or -LAML is not minimized, the step is halved until it is.

**Usage**

```r
NR.rho(
  build, rho.ini, data, formula, max.it.beta = 200, max.it.rho = 30, beta.ini = NULL, detail.rho = FALSE, detail.beta = FALSE, nb.smooth, tol.beta = 1e-04,
```

NR.rho

```r
tol.rho = 1e-04,
step.max = 5,
method = "LAML"
```

Arguments

- **build**: list of objects returned by `model.cons`
- **rho.ini**: vector of initial log smoothing parameters; if it is NULL, all log lambda are set to -1
- **data**: an optional data frame containing the variables in the model
- **formula**: formula object specifying the model
- **max.it.beta**: maximum number of iterations to reach convergence in the regression parameters; default is 200
- **max.it.rho**: maximum number of iterations to reach convergence in the smoothing parameters; default is 30
- **beta.ini**: vector of initial regression parameters; default is NULL, in which case the first beta will be \( \log(\text{sum(event)}/\text{sum(t1)}) \) and the others will be zero (except if there are "by" variables in which case all betas are set to zero)
- **detail.rho**: if TRUE, details concerning the optimization process in the smoothing parameters are displayed; default is FALSE
- **detail.beta**: if TRUE, details concerning the optimization process in the regression parameters are displayed; default is FALSE
- **nb.smooth**: number of smoothing parameters
- **tol.beta**: convergence tolerance for regression parameters; default is 1e-04
- **tol.rho**: convergence tolerance for smoothing parameters; default is 1e-04
- **step.max**: maximum absolute value possible for any component of the step vector (on the log smoothing parameter scale); default is 5
- **method**: LCV or LAML; default is LAML

Details

If we note `val` the current LCV or LAML value, `val.old` the previous one and `grad` the gradient vector of LCV or LAML with respect to the log smoothing parameters, the algorithm goes on while(`abs(val-val.old)>tol.rho|any(abs(grad)>tol.rho))

Value

object of class survPen (see `survPen.fit` for details)

Examples

```r
library(survPen)

# standard spline of time with 4 knots
```
data <- data.frame(time=seq(0,5,length=100),event=1,t0=0)

form <- ~ smf(time,knots=c(0,1,3,5))

t1 <- eval(substitute(time), data)
t0 <- eval(substitute(t0), data)
event <- eval(substitute(event), data)

# Setting up the model before fitting
model.c <- model.cons(form,lambda=0,data.spec=data,t1=t1,t1.name="time",
t0=rep(0,100),t0.name="t0",event=event,event.name="event",
expected=0,expected.name=NULL,type="overall",n.legendre=20,
c1="survPen(form,data,t1=time, event=event)",beta.ini=NULL)

# Estimating the smoothing parameter and the regression parameters
# we need to apply a reparameterization to model.c before fitting
Newton2 <- NR.rho(repam(model.c)$build,rho.ini=-1,data,form,nb.smooth=1,detail.rho=TRUE)

---

**predict.survPen**

**Hazard and Survival prediction from fitted survPen model**

**Description**

Takes a fitted survPen object and produces hazard and survival predictions given a new set of values for the model covariates.

**Usage**

```r
## S3 method for class 'survPen'
predict(
  object,
  newdata,
  newdata.ref = NULL,
  n.legendre = 50,
  conf.int = 0.95,
  do.surv = TRUE,
  type = "standard",
  exclude.random = FALSE,
  get.deriv.H = FALSE,
  ...
)
```

**Arguments**

- `object` a fitted survPen object as produced by `survPen.fit`
- `newdata` data frame giving the new covariates value
predict.survPen

newdata.ref: data frame giving the new covariates value for the reference population (used only when type="HR")

n.legendre: number of nodes to approximate the cumulative hazard by Gauss-Legendre quadrature; default is 50

conf.int: numeric value giving the precision of the confidence intervals; default is 0.95

do.surv: If TRUE, the survival and its lower and upper confidence values are computed. Survival computation requires numerical integration and can be time-consuming so if you only want the hazard use do.surv=FALSE; default is TRUE

type: if type="lpmatrix" returns the design matrix (or linear predictor matrix) corresponding to the new values of the covariates; if equals "HR", returns the predicted HR and CIs between newdata and newdata.ref; default is "standard" for classical hazard and survival estimation

exclude.random: if TRUE all random effects are set to zero; default is FALSE

get.deriv.H: if TRUE, the derivatives wrt to the regression parameters of the cumulative hazard are returned; default is FALSE

... other arguments

Details

The confidence intervals noted CI.U are built on the log cumulative hazard scale U=log(H) (efficient scale in terms of respect towards the normality assumption) using Delta method. The confidence intervals on the survival scale are then CI.surv = exp(-exp(CI.U))

Value

List of objects:

haz: hazard predicted by the model

haz.inf: lower value for the confidence interval on the hazard based on the Bayesian covariance matrix Vp (Wood et al. 2016)

haz.sup: Upper value for the confidence interval on the hazard based on the Bayesian covariance matrix Vp

surv: survival predicted by the model

surv.inf: lower value for the confidence interval on the survival based on the Bayesian covariance matrix Vp

surv.sup: Upper value for the confidence interval on the survival based on the Bayesian covariance matrix Vp

deriv.H: derivatives wrt to the regression parameters of the cumulative hazard. Useful to calculate standardized survival

HR: predicted hazard ratio; only when type = "HR"

HR.inf: lower value for the confidence interval on the hazard ratio based on the Bayesian covariance matrix Vp; only when type = "HR"

HR.sup: Upper value for the confidence interval on the hazard ratio based on the Bayesian covariance matrix Vp; only when type = "HR"
References


Examples

library(survPen)

data(datCancer) # simulated dataset with 2000 individuals diagnosed with cervical cancer

# model : unidimensional penalized spline for time since diagnosis with 5 knots
f1 <- ~smf(fu,df=5)

# hazard model
mod1 <- survPen(f1,data=datCancer,t1=fu,event=dead,expected=NULL,method="LAML")

# predicting hazard and survival at time 1
pred <- predict(mod1,data.frame(fu=1))
pred$haz
pred$surv

# predicting hazard ratio between age 70 and age 30
pred.HR <- predict(mod1,data.frame(fu=1,age=70),newdata.ref=data.frame(fu=1,age=30),type="HR")
pred.HR$HR
pred.HR$HR.inf
pred.HR$HR.sup

print.summary.survPen

Description

print summary for a survPen fit

Usage

## S3 method for class 'summary.survPen'
print(
  x,
  digits = max(3,getOption("digits") - 2),
  signif.stars = getOption("show.signif.stars"),
  ...
)
Arguments

- **x**: an object of class `summary.survPen`
- **digits**: controls number of digits printed in output.
- **signif.stars**: Should significance stars be printed alongside output.
- **...**: other arguments

Value

- print of summary

---

**rd**

*Defining random effects in survPen formulae*

Description

Used inside a formula object to define a random effect.

Usage

```r
rd(...)```

Arguments

- **...**: Any number of covariates separated by "," 

Value

- object of class `rd.smooth.spec`

Examples

```
# cubic regression spline of time with 10 unspecified knots + random effect at the cluster level
formula.test <- ~smf(time,df=10) + rd(cluster)
```
Applies initial reparameterization for stable evaluation of the log determinant of the penalty matrix

Description

Transforms the object from \texttt{model.cons} by applying the matrix reparameterization (matrix U.F). The reparameterization is reversed at convergence by \texttt{inv.repam}.

Usage

\texttt{repam(build)}

Arguments

\begin{itemize}
  \item \texttt{build} \hspace{1cm} \texttt{object as returned by model.cons}
\end{itemize}

Value

\begin{itemize}
  \item \texttt{build} \hspace{1cm} \texttt{an object as returned by model.cons}
  \item \texttt{X.ini} \hspace{1cm} \texttt{initial design matrix (before reparameterization)}
  \item \texttt{S.pen.ini} \hspace{1cm} \texttt{initial penalty matrices}
\end{itemize}

Examples

\begin{verbatim}
library(survPen)

# standard spline of time with 4 knots
data <- data.frame(time=seq(0,5,length=100),event=1,t0=0)
form <- ~ smf(time,knots=c(0,1,3,5))
t1 <- eval(substitute(time), data)
t0 <- eval(substitute(t0), data)
event <- eval(substitute(event), data)

# Setting up the model before fitting
model.c <- model.cons(form,lambda=0,data.spec=data,t1=t1,t1.name="time",
t0=rep(0,100),t0.name="t0",event=event,event.name="event",
expected=NULL,expected.name=NULL,type="overall",n.legendre=20,
cl="survPen(form,data,t1=time,event=event)",beta.ini=NULL)

# Reparameterization allows separating the parameters into unpenalized and
# penalized ones for maximum numerical stability
re.model.c <- repam(model.c)
\end{verbatim}
**smf**

*Defining smooths in survPen formulae*

**Description**

Used inside a formula object to define a smooth, a tensor product smooth or a tensor product interaction. Natural cubic regression splines (linear beyond the knots, equivalent to `ns` from package `splines`) are used as marginal bases. While `tensor` builds a tensor product of marginal bases including the intercepts, `tint` applies a tensor product of the marginal bases without their intercepts. Unlike `tensor`, the marginal effects of the covariates should also be present in the formula when using `tint`. For a conceptual difference between tensor products and tensor product interactions see Section 5.6.3 from Wood (2017)

**Usage**

```r
smf(..., knots = NULL, df = NULL, by = NULL, same.rho = FALSE)
tensor(..., knots = NULL, df = NULL, by = NULL, same.rho = FALSE)
tint(..., knots = NULL, df = NULL, by = NULL, same.rho = FALSE)
```

**Arguments**

- `...` Any number of covariates separated by ","
- `knots` numeric vector that specifies the knots of the splines (including boundaries); default is `NULL`, in which case the knots are spread through the covariate values using quantiles. Precisely, for the term "smf(x,df=df1)", the vector of knots will be: `quantile(unique(x),seq(0,1,length=df1))`
- `df` numeric value that indicates the number of knots (or degrees of freedom) desired; default is `NULL`. If `knots` and `df` are `NULL`, `df` will be set to 10
- `by` numeric or factor variable in order to define a varying coefficient smooth
- `same.rho` if the specified by variable is a factor, specifies whether the smoothing parameters should be the same for all levels; default is `FALSE`.

**Value**

object of class `smf.smooth.spec`, `tensor.smooth.spec` or `tint.smooth.spec` (see `smooth.spec` for details)

**References**

Examples

# penalized cubic regression spline of time with 5 unspecified knots
formula.test <- ~smf(time,df=5)

# suppose that we want to fit a model from formula.test
library(survPen)
data(datCancer)

mod.test <- survPen(~smf(fu,df=5),data=datCancer,t1=fu,event=dead)

# then the knots can be retrieved like this:
mod.test$list.smf[[1]]$knots
# or calculated like this
quantile(unique(datCancer$fu),seq(0,1,length=5))

# penalized cubic regression splines of time and age with respectively 5 and 7 unspecified knots
formula.test2 <- ~smf(time,df=5)+smf(age,df=7)

# penalized cubic regression splines of time and age with respectively 3 and 4 specified knots
formula.test3 <- ~smf(time, knots=c(0,3,5))+smf(age, knots=c(30,50,70,90))

# penalized tensor product for time and age with respectively 5 and 4 unspecified knots leading # to 5*4 = 20 regression parameters
formula.test <- ~tensor(time, age, df=c(5,4))

# penalized tensor product for time and age with respectively 3 and 4 specified knots
formula.test3 <- ~tensor(time, age, df=c(30,50,70,90))

# penalized tensor product for time, age and year with respectively 6, 5 and 4 unspecified knots
formula.test <- ~tensor(time, age, year, df=c(6,5,4))

# penalized tensor product interaction for time and age with respectively 5 and 4 unspecified knots # main effects are specified as penalized cubic regression splines
formula.test <- ~smf(time,df=5)+smf(age,df=4)+tint(time,age,df=c(5,4))

smooth.cons Design and penalty matrices of penalized splines in a smooth.spec object

Description

Builds the design and penalty matrices from the result of smooth.spec.

Usage

smooth.cons(
  term,
smooth.cons

knots,
  df,
  by = NULL,
  option,
  data.spec,
  same.rho = FALSE,
  name
)

Arguments

term Vector of strings that generally comes from the value "term" of a smooth.spec object.
knots List of numeric vectors that specifies the knots of the splines (including boundaries).
df Degrees of freedom: numeric vector that indicates the number of knots desired for each covariate.
by numeric or factor variable in order to define a varying coefficient smooth; default is NULL.
onlineation "smf", "tensor" or "tint".
data.spec data frame that represents the environment from which the covariate values and knots are to be calculated; default is NULL.
same.rho if there is a factor by variable, should the smoothing parameters be the same for all levels; default is FALSE.
name simplified name of the smooth.spec call.

Value

List of objects with the following items:

X Design matrix
ten List of penalty matrices
term Vector of strings giving the names of each covariate
knots list of numeric vectors that specifies the knots for each covariate
dim Number of covariates
all.df Numeric vector giving the number of knots associated with each covariate
sum.df Sum of all.df
Z.smf List of matrices that represents the sum-to-zero constraint to apply for "smf" splines
Z.tensor List of matrices that represents the sum-to-zero constraint to apply for "tensor" splines
Z.tint List of matrices that represents the sum-to-zero constraint to apply for "tint" splines
lambda.name name of the smoothing parameters
Examples

library(survPen)

# standard spline of time with 4 knots (so we get a design matrix with 3 columns
# because of centering constraint)

data <- data.frame(time=seq(0,5,length=100))
smooth.c <- smooth.cons("time",knots=list(c(0,1,3,5)),df=4,option="smf",
data.spec=data,name="smf(time)"

smooth.cons.integral

Design matrix of penalized splines in a smooth.spec object for Gauss-Legendre quadrature

Description

Almost identical to smooth.cons. This version is dedicated to Gauss-Legendre quadrature. Here, the sum-to-zero constraints must be specified so that they correspond to the ones that were calculated with the initial dataset.

Usage

smooth.cons.integral(
  term,
  knots,
  df,
  by = NULL,
  option,
  data.spec,
  Z.smf,
  Z.tensor,
  Z.tint,
  name
)

Arguments

term Vector of strings that generally comes from the value "term" of a smooth.spec object
knots List of numeric vectors that specifies the knots of the splines (including boundaries).
df Degrees of freedom : numeric vector that indicates the number of knots desired for each covariate.
by numeric or factor variable in order to define a varying coefficient smooth; default is NULL.
smooth.spec

Description

Specifies the covariates to be considered as penalized splines.

Usage

smooth.spec(
    ...,
    knots = NULL,
    df = NULL,
by = NULL,
option = NULL,
same.rho = FALSE
)

Arguments

... Numeric vectors specified in smf, tensor or tint
knots List of numeric vectors that specifies the knots of the splines (including boundaries); default is NULL
df Degrees of freedom: numeric vector that indicates the number of knots desired for each covariate; default is NULL
by numeric or factor variable in order to define a varying coefficient smooth; default is NULL
option "smf", "tensor" or "tint". Depends on the wrapper function; default is "smf"
same.rho if there is a factor by variable, should the smoothing parameters be the same for all levels; default is FALSE.

Value

object of class smooth.spec
term Vector of strings giving the names of each covariate specified in ...
dim Numeric value giving the number of covariates associated with this spline
knots list of numeric vectors that specifies the knots for each covariate
df Numeric vector giving the number of knots associated with each covariate
by numeric or factor variable in order to define a varying coefficient smooth
same.rho if there is a factor by variable, should the smoothing parameters be the same for all levels; default is FALSE
name simplified name of the call to function smooth.spec

Examples

library(survPen)

# standard spline of time with 10 unspecified knots
smooth.spec(time)

# tensor of time and age with 5x5 specified knots
smooth.s <- smooth.spec(time, age, knots=list(time=seq(0,5,length=5), age=seq(20,80,length=5)),
option="tensor")
summary.survPen

Summary for a survPen fit

Description
Takes a fitted survPen object and produces various useful summaries from it.

Usage
```r
## S3 method for class 'survPen'
summary(object, ...)
```

Arguments
- `object`: a fitted survPen object as produced by `survPen.fit`
- `...`: other arguments

Value
List of objects:
- `call`: the original survPen call
- `formula`: the original survPen formula
- `coefficients`: reports the regression parameters estimates for unpenalized terms with the associated standard errors
- `edf.per.smooth`: reports the edf associated with each smooth term
- `random`: TRUE if there are random effects in the model
- `random.effects`: reports the estimates of the log standard deviation (log(sd)) of every random effects plus the estimated standard error (also on the log(sd) scale)
- `likelihood`: unpenalized likelihood of the model
- `penalizedlikelihood`: penalized likelihood of the model
- `nb.smooth`: number of smoothing parameters
- `smoothing.parameter`: smoothing parameters estimates
- `parameters`: number of regression parameters
- `edf`: effective degrees of freedom
- `method`: smoothing selection criterion used (LAML or LCV)
- `val.criterion`: minimized value of criterion. For LAML, what is reported is the negative log marginal likelihood
- `converged`: convergence indicator, TRUE or FALSE. TRUE if Hess.beta.modif=FALSE and Hess.rho.modif=FALSE (or NULL)
Examples

```
library(survPen)

data(datCancer) # simulated dataset with 2000 individuals diagnosed with cervical cancer

# model: unidimensional penalized spline for time since diagnosis with 5 knots
f1 <- ~smf(fu,df=5)

# fitting hazard model
mod1 <- survPen(f1,data=datCancer,t1=fu,event=dead,expected=NULL,method="LAML")

# summary
summary(mod1)
```

---

**survPen** *(Excess) hazard model with (multidimensional) penalized splines and integrated smoothness estimation*

---

**Description**

Fits an (excess) hazard model with (multidimensional) penalized splines allowing for time-dependent effects, non-linear effects and interactions between several continuous covariates. The linear predictor is specified on the logarithm of the (excess) hazard. Smooth terms are represented using cubic regression splines with associated quadratic penalties. For multidimensional smooths, tensor product splines or tensor product interactions are available. Smoothness is estimated automatically by optimizing one of two criteria: Laplace approximate marginal likelihood (LAML) or likelihood cross-validation (LCV). When specifying the model’s formula, no distinction is made between the part relative to the form of the baseline hazard and the one relative to the effects of the covariates. Thus, time-dependent effects are naturally specified as interactions with some function of time via "*" or ":". See the examples below for more details. The main functions of the survPen package are `survPen`, `smf`, `tensor`, `tint` and `rd`. The first one fits the model while the other four are constructors for penalized splines.

The user must be aware that the survPen package does not depend on mgcv. Thus, all the functionalities available in mgcv in terms of types of splines (such as thin plate regression splines or P-splines) are not available in survPen (yet).

**Usage**

```
survPen(
  formula, 
  data, 
  t1, 
  t0 = NULL, 
  event, 
  expected = NULL, 
```
survPen

lambda = NULL,
rho.ini = NULL,
max.it.beta = 200,
max.it.rho = 30,
beta.ini = NULL,
detail.rho = FALSE,
detail.beta = FALSE,
n.legrendre = 20,
method = "LAML",
tol.beta = 1e-04,
tol.rho = 1e-04,
step.max = 5
)

Arguments

formula formula object specifying the model. Penalized terms are specified using smf (comparable to s(...,bs="cr") in mgcv), tensor (comparable to te(...,bs="cr") in mgcv), tint (comparable to ti(...,bs="cr") in mgcv), or rd (comparable to s(...,bs="re") in mgcv).
data an optional data frame containing the variables in the model
t1 vector of follow-up times or name of the column in data containing follow-up times
t0 vector of origin times or name of the column in data containing origin times; allows to take into account left truncation; default is NULL, in which case it will be a vector of zeroes
event vector of right-censoring indicators or name of the column in data containing right-censoring indicators; 1 if the event occurred and 0 otherwise
expected (for net survival only) vector of expected hazard or name of the column in data containing expected hazard; default is NULL, in which case overall survival will be estimated
lambda vector of smoothing parameters; default is NULL when it is to be estimated by LAML or LCV
rho.ini vector of initial log smoothing parameters; default is NULL, in which case every initial log lambda will be -1
max.it.beta maximum number of iterations to reach convergence in the regression parameters; default is 200
max.it.rho maximum number of iterations to reach convergence in the smoothing parameters; default is 30
beta.ini vector of initial regression parameters; default is NULL, in which case the first beta will be \( \log(\text{sum(event)}/\text{sum(t1)}) \) and the others will be zero (except if there are "by" variables in which case all betas are set to zero)
detail.rho if TRUE, details concerning the optimization process in the smoothing parameters are displayed; default is FALSE
detail.beta if TRUE, details concerning the optimization process in the regression parameters are displayed; default is FALSE
The **survPen** function implements the framework described by Wood et al. (2016) for modelling time-to-event data without requiring data splitting and Poisson likelihood approximation. The effects of continuous covariates are represented using low rank spline bases with associated quadratic penalties. The **survPen** function allows to account simultaneously for time-dependent effects, non-linear effects and interactions between several continuous covariates without the need to build a possibly demanding model-selection procedure. Besides LAML, a likelihood cross-validation (LCV) criterion (O’Sullivan 1988) can be used for smoothing parameter estimation. First and second derivatives of LCV with respect to the smoothing parameters are implemented so that LCV optimization is computationally equivalent to the LAML optimization proposed by Wood et al. (2016). In practice, LAML optimization is generally both a bit faster and a bit more stable so it is used as default. For \(m\) covariates \((x_1, \ldots, x_m)\), if we note \(h(t, x_1, \ldots, x_m)\) the hazard at time \(t\), the hazard model is the following:

\[
\log[h(t, x_1, \ldots, x_m)] = \sum_j g_j(t, x_1, \ldots, x_m)
\]

where each \(g_j\) is either the marginal basis of a specific covariate or a tensor product smooth of any number of covariates. The marginal bases of the covariates are represented as natural (or restricted) cubic splines (as in function `ns` from library `splines`) with associated quadratic penalties. Full parametric (unpenalized) terms for the effects of covariates are also possible (see the examples below). Each \(g_j\) is then associated with zero, one or several smoothing parameters. The estimation procedure is based on outer Newton-Raphson iterations for the smoothing parameters and on inner Newton-Raphson iterations for the regression parameters (see Wood et al. 2016). Estimation of the regression parameters in the inner algorithm is by direct maximization of the penalized likelihood of the survival model, therefore avoiding data augmentation and Poisson likelihood approximation.
The cumulative hazard included in the log-likelihood is approximated by Gauss-Legendre quadrature for numerical stability.

**Value**

Object of class "survPen" (see `survPenObject` for details)

**by variables**

The `smf`, `tensor` and `tint` terms used to specify smooths accept an argument `by`. This by argument allows for building varying-coefficient models i.e. for letting smooths interact with factors or parametric terms. If a `by` variable is numeric, then its `i`th element multiplies the `i`th row of the model matrix corresponding to the smooth term concerned. If a `by` variable is a factor then it generates an indicator vector for each level of the factor, unless it is an ordered factor. In the non-ordered case, the model matrix for the smooth term is then replicated for each factor level, and each copy has its rows multiplied by the corresponding rows of its indicator variable. The smoothness penalties are also duplicated for each factor level. In short a different smooth is generated for each factor level. The main interest of `by` variables over separated models is the same. The `rho` argument (for `smf`, `tensor` and `tint`) which allows forcing all smooths to have the same smoothing parameter(s). Ordered `by` variables are handled in the same way, except that no smooth is generated for the first level of the ordered factor. This is useful if you are interested in differences from a reference level. See the `survPen` vignette for more details.

**Random effects**

i.i.d random effects can be specified using penalization. Indeed, the ridge penalty is equivalent to an assumption that the regression parameters are i.i.d. normal random effects. Thus, it is easy to fit a frailty hazard model. For example, consider the model term `rd(clust)` which will result in a model matrix component corresponding to `model.matrix(~clust-1)` being added to the model matrix for the whole model. The associated regression parameters are assumed i.i.d. normal, with unknown variance (to be estimated). This assumption is equivalent to an identity penalty matrix (i.e. a ridge penalty) on the regression parameters. The unknown smoothing parameter $\lambda$ associated with the term `rd(clust)` is directly linked to the unknown variance $\sigma^2$: $\sigma^2 = \frac{1}{\lambda * S.scale}$. Then, the estimated log standard deviation is: $\log(\hat{\sigma}) = -0.5 * \log(\hat{\lambda}) - 0.5 * \log(S.scale)$. And the estimated variance of the log standard deviation is: $Var[\log(\hat{\sigma})] = 0.25 * Var[\log(\hat{\lambda})] = 0.25 * inv.Hess.rho$. See the `survPen` vignette for more details. This approach allows implementing commonly used random effect structures. For example if `g` is a factor then `rd(g)` produces a random parameter for each level of `g`, the random parameters being i.i.d. normal. If `g` is a factor and `x` is numeric, then `rd(g,x)` produces an i.i.d. normal random slope relating the response to `x` for each level of `g`. Thus, random effects treated as penalized splines allow specifying frailty (excess) hazard models (Charvat et al. 2016). For each individual `i` from cluster (usually geographical unit) `j`, a possible model would be:

$$ log[h(t_{ij}, x_{ij1}, \ldots, x_{ijm})] = \sum_k g_k(t_{ij}, x_{ij1}, \ldots, x_{ijm}) + w_j $$

where $w_j$ follows a normal distribution with mean 0. The random effect associated with the cluster variable is specified with the model term `rd(cluster)`. We could also specify a random effect
depending on age for example with the model term \( \text{rd(cluster, age)} \). \( u_j = \exp(w_j) \) is known as the shared frailty.

See the survival_analysis_with_survPen vignette for more details.

Excess hazard model

When studying the survival of patients who suffer from a common pathology we may be interested in the concept of excess mortality that represents the mortality due to that pathology. For example, in cancer epidemiology, individuals may die from cancer or from another cause. The problem is that the cause of death is often either unavailable or unreliable. Supposing that the mortality due to other causes may be obtained from the total mortality of the general population (called expected mortality for cancer patients), we can define the concept of excess mortality. The excess mortality is directly linked to the concept of net survival, which would be the observed survival if patients could not die from other causes. Therefore, when such competing events are present, one may choose to fit an excess hazard model instead of a classical hazard model. Flexible excess hazard models have already been proposed (for examples see Remontet et al. 2007, Charvat et al. 2016) but none of them deals with a penalized framework (in a non-fully Bayesian setting). Excess mortality can be estimated supposing that, in patients suffering from a common pathology, mortality due to other causes than the pathology can be obtained from the (all cause) mortality of the general population; the latter is referred to as the expected mortality \( h_P \). The mortality observed in the patients (\( h_O \)) is actually decomposed as the sum of \( h_P \) and the excess mortality due to the pathology (\( h_E \)). This may be written as:

\[
h_O(t,x) = h_E(t,x) + h_P(a + t, z)
\]

In that equation, \( t \) is the time since cancer diagnosis, \( a \) is the age at diagnosis, \( h_P \) is the mortality of the general population at age \( a + t \) given demographical characteristics \( z \) (\( h_P \) is considered known and available from national statistics), and \( x \) a vector of variables that may have an effect on \( h_E \).

Including the age in the model is necessary in order to deal with the informative censoring due to other causes of death. Thus, for \( m \) covariates \( (x_1, \ldots, x_m) \), if we note \( h_E(t, x_1, \ldots, x_m) \) the excess hazard at time \( t \), the excess hazard model is the following:

\[
\log[h_E(t, x_1, \ldots, x_m)] = \sum_j g_j(t, x_1, \ldots, x_m)
\]

Convergence

No convergence indicator is given. If the function returns an object of class survPen, it means that the algorithm has converged. If convergence issues occur, an error message is displayed. If convergence issues occur, do not refrain to use detail.rho and/or detail.beta to see exactly what is going on in the optimization process. To achieve convergence, consider lowering step.max and/or changing rho.ini and beta.ini. If your excess hazard model fails to converge, consider fitting a hazard model and use its estimated parameters as initial values for the excess hazard model. Finally, do not refrain to change the "method" argument (LCV or LAML) if convergence issues occur.

Other

Be aware that all character variables are transformed to factors before fitting.
References

Charvat, H., Remontet, L., Bossard, N., Roche, L., Dejardin, O., Rachet, B., ... and Belot, A. (2016), A multilevel excess hazard model to estimate net survival on hierarchical data allowing for non linear and non proportional effects of covariates. Statistics in medicine, 35(18), 3066-3084.


Examples

```r
library(survPen)
data(datCancer) # simulated dataset with 2000 individuals diagnosed with cervical cancer

#-------------------------------------------------------- example 0
# Comparison between restricted cubic splines and penalized restricted cubic splines
library(splines)

# unpenalized
f <- ~ns(fu,knots=c(0.25, 0.5, 1, 2, 4),Boundary.knots=c(0,5))
mod <- survPen(f,data=datCancer,t1=fu,event=dead)

# penalized
f.pen <- ~ smf(fu,knots=c(0,0.25, 0.5, 1, 2, 4,5)) # careful here: the boundary knots are included
mod.pen <- survPen(f.pen,data=datCancer,t1=fu,event=dead)
```
# predictions

new.time <- seq(0,5,length=100)
pred <- predict(mod,data.frame(fu=new.time))
pred.pen <- predict(mod.pen,data.frame(fu=new.time))

par(mfrow=c(1,1))
plot(new.time,pred$haz,type="l",ylim=c(0,0.2),main="hazard vs time",
xlab="time since diagnosis (years)",ylab="hazard",col="red")
lines(new.time,pred.pen$haz,col="blue3")
legend("topright",legend=c("unpenalized","penalized"),
col=c("red","blue3"),lty=rep(1,2))

#-------------------------------------------------------- example 1
# hazard models with unpenalized formulas compared to a penalized tensor product smooth

library(survPen)
data(datCancer) # simulated dataset with 2000 individuals diagnosed with cervical cancer

# constant hazard model
f.cst <- ~1
mod.cst <- survPen(f.cst,data=datCancer,t1=fu,event=dead)

# piecewise constant hazard model
f.pwcst <- ~cut(fu,breaks=seq(0,5,by=0.5),include.lowest=TRUE)
mod.pwcst <- survPen(f.pwcst,data=datCancer,t1=fu,event=dead,n.legendre=200)
# we increase the number of points for Gauss-Legendre quadrature to make sure that the cumulative
# hazard is properly approximated

# linear effect of time
f.lin <- ~fu
mod.lin <- survPen(f.lin,data=datCancer,t1=fu,event=dead)

# linear effect of time and age with proportional effect of age
f.lin.age <- ~fu+age
mod.lin.age <- survPen(f.lin.age,data=datCancer,t1=fu,event=dead)

# linear effect of time and age with time-dependent effect of age (linear)
f.lin.inter.age <- ~fu*age
mod.lin.inter.age <- survPen(f.lin.inter.age,data=datCancer,t1=fu,event=dead)

# cubic B-spline of time with a knot at 1 year, linear effect of age and time-dependent effect
# of age with a quadratic B-spline of time with a knot at 1 year
library(splines)
f.spline.inter.age <- ~bs(fu,knots=c(1),Boundary.knots=c(0,5))+age+
age:bs(fu,knots=c(1),Boundary.knots=c(0,5),degree=2)
# here, bs indicates an unpenalized cubic spline
mod.spline.inter.age <- survPen(f.spline.inter.age,data=datCancer,t1=fu,event=dead)
# tensor of time and age

def tensor <- ~tensor(fu, age)

mod.tensor <- survPen(f.tensor, data=datCancer, t1=fu, event=dead)

# predictions of the models at age 60

new.time <- seq(0,5, length=100)
pred.cst <- predict(mod.cst, data.frame(fu=new.time))
pred.pwcst <- predict(mod.pwcst, data.frame(fu=new.time))
pred.lin <- predict(mod.lin, data.frame(fu=new.time))
pred.lin.age <- predict(mod.lin.age, data.frame(fu=new.time, age=60))
pred.lin.inter.age <- predict(mod.lin.inter.age, data.frame(fu=new.time, age=60))
pred.spline.inter.age <- predict(mod.spline.inter.age, data.frame(fu=new.time, age=60))
pred.tensor <- predict(mod.tensor, data.frame(fu=new.time, age=60))

lwd1 <- 2

par(mfrow=c(1,1))
plot(new.time, pred.cst$haz, type="l", ylim=c(0, 0.2), main="hazard vs time",
xlab="time since diagnosis (years)", ylab="hazard", col="blue3", lwd=lwd1)
segments(x0=new.time[1:99], x1=new.time[2:100], y0=pred.pwcst$haz[1:99], col="lightblue2", lwd=lwd1)
lines(new.time, pred.lin$haz, col="green3", lwd=lwd1)
lines(new.time, pred.lin.age$haz, col="yellow", lwd=lwd1)
lines(new.time, pred.lin.inter.age$haz, col="orange", lwd=lwd1)
lines(new.time, pred.spline.inter.age$haz, col="red", lwd=lwd1)
lines(new.time, pred.tensor$haz, col="black", lwd=lwd1)
legend("topright",
legend=c("cst", "pwcst", "lin", "lin.age", "lin.inter.age", "spline.inter.age", "tensor"),
col=c("blue3", "lightblue2", "green3", "yellow", "orange", "red", "black"),
lty=rep(1,7), lwd=rep(lwd1,7))

# you can also calculate the hazard yourself with the lpmatrix option.
# For example, compare the following predictions:

haz.tensor <- pred.tensor$haz

X.tensor <- predict(mod.tensor, data.frame(fu=new.time, age=60), type="lpmatrix")
haz.tensor.lpmatrix <- exp(X.tensor%*%mod.tensor$coefficients)

summary(haz.tensor.lpmatrix - haz.tensor)

#---------------- The 95% confidence intervals can be calculated like this:

# standard errors from the Bayesian covariance matrix Vp
std <- sqrt(rowSums((X.tensor%*%mod.tensor$Vp)*X.tensor))

qt.norm <- stats::qnorm(1-(1-0.95)/2)
haz.inf <- as.vector(exp(X.tensor%*%mod.tensor$coefficients-qt.norm*std))
haz.sup <- as.vector(exp(X.tensor%*%mod.tensor$coefficients+qt.norm*std))

# checking that they are similar to the ones given by the predict function
summary(haz.inf - pred.tensor$haz.inf)
# Example 2

```r
library(survPen)
data(datCancer) # simulated dataset with 2000 individuals diagnosed with cervical cancer

# model: unidimensional penalized spline for time since diagnosis with 5 knots
f1 <- ~smf(fu, df=5)
# when knots are not specified, quantiles are used. For example, for the term "smf(x, df=df1)",
# the vector of knots will be: quantile(unique(x), seq(0,1, length=df1))

# you can specify your own knots if you want
# f1 <- ~smf(fu, knots=c(0,1,3,6,8))

# hazard model
mod1 <- survPen(f1, data=datCancer, t1=fu, event=dead, expected=NULL, method="LAML")
summary(mod1)

# to see where the knots were placed
mod1$list.smf

# with LCV instead of LAML
mod1bis <- survPen(f1, data=datCancer, t1=fu, event=dead, expected=NULL, method="LCV")
summary(mod1bis)

# hazard model taking into account left truncation (not representative of cancer data,
# the begin variable was simulated for illustration purposes only)
mod2 <- survPen(f1, data=datCancer, t0=begin, t1=fu, event=dead, expected=NULL, method="LAML")
summary(mod2)

# excess hazard model
mod3 <- survPen(f1, data=datCancer, t1=fu, event=dead, expected=rate, method="LAML")
summary(mod3)

# compare the predictions of the models
new.time <- seq(0, 5, length=50)
pred1 <- predict(mod1, data.frame(fu=new.time))
pred1bis <- predict(mod1bis, data.frame(fu=new.time))
pred2 <- predict(mod2, data.frame(fu=new.time))
pred3 <- predict(mod3, data.frame(fu=new.time))

# LAML vs LCV
par(mfrow=c(1,2))
plot(new.time, pred1$haz, type="l", ylim=c(0, 0.2), main="LCV vs LAML",
     xlab="time since diagnosis (years)", ylab="hazard")
lines(new.time, pred1bis$haz, col="blue3")
legend("topright", legend=c("LAML", "LCV"), col=c("black", "blue3"), lty=c(1,1))

plot(new.time, pred1$surv, type="l", ylim=c(0,1), main="LCV vs LAML",
     xlab="time since diagnosis (years)", ylab="survival")
lines(new.time, pred1bis$surv, col="blue3")
```
# hazard vs excess hazard
par(mfrow=c(1,2))
plot(new.time,pred1$haz,type="l",ylim=c(0,0.2),main="hazard vs excess hazard",
 xlab="time since diagnosis (years)",ylab="hazard")
lines(new.time,pred3$haz,col="green3")
legend("topright",legend=c("overall","excess"),col=c("black","green3"),lty=c(1,1))

plot(new.time,pred1$surv,type="l",ylim=c(0,1),main="survival vs net survival",
 xlab="time",ylab="survival")
lines(new.time,pred3$surv,col="green3")
legend("topright",legend=c("overall survival","net survival"),col=c("black","green3"),lty=c(1,1))

# hazard vs excess hazard with 95% Bayesian confidence intervals (based on Vp matrix,
# see predict.survPen)
par(mfrow=c(1,1))
plot(new.time,pred1$haz,type="l",ylim=c(0,0.2),main="hazard vs excess hazard",
 xlab="time since diagnosis (years)",ylab="hazard")
lines(new.time,pred1$haz.inf,lty=2)
lines(new.time,pred1$haz.sup,lty=2)
lines(new.time,pred3$haz.inf,lty=2,col="green3")
lines(new.time,pred3$haz.sup,lty=2,col="green3")

#-------------------------------------------------------- example 3
library(survPen)
data(datCancer) # simulated dataset with 2000 individuals diagnosed with cervical cancer

# models: tensor product smooth vs tensor product interaction of time since diagnosis and
# age at diagnosis. Smoothing parameters are estimated via LAML maximization
f2 <- ~tensor(fu,age,df=c(5,5))
f3 <- ~tint(fu,df=5)+tint(age,df=5)+tint(fu,age,df=c(5,5))

# hazard model
mod4 <- survPen(f2,data=datCancer,t1=fu,event=dead)
summary(mod4)

mod5 <- survPen(f3,data=datCancer,t1=fu,event=dead)
summary(mod5)

# predictions
new.age <- seq(50,90,length=50)
new.time <- seq(0,7,length=50)
Z4 <- outer(new.time,new.age,function(t,a) predict(mod4,data.frame(fu=t,age=a))$haz)
Z5 <- outer(new.time,new.age,function(t,a) predict(mod5,data.frame(fu=t,age=a))$haz)

# color settings
col.pal <- colorRampPalette(c("white", "red"))
colors <- col.pal(100)

facet <- function(z){
  facet.center <- (z[-1, -1] + z[-1, -ncol(z)] + z[-nrow(z), -1] + z[-nrow(z), -ncol(z)])/4
cut(facet.center, 100)
}

# plot the hazard surfaces for both models
par(mfrow=c(1,2))
persp(new.time,new.age,Z4,col=colors[facet(Z4)],main="tensor",theta=30,
  xlab="time since diagnosis",ylab="age at diagnosis",zlab="excess hazard",ticktype="detailed")
persp(new.time,new.age,Z5,col=colors[facet(Z5)],main="tint",theta=30,
  xlab="time since diagnosis",ylab="age at diagnosis",zlab="excess hazard",ticktype="detailed")

#-------------------------------------------------------- example 4
library(survPen)
data(datCancer) # simulated dataset with 2000 individuals diagnosed with cervical cancer

# model : tensor product spline for time, age and yod (year of diagnosis)
# yod is not centered here since it does not create unstability but be careful in practice
# and consider centering your covariates if you encounter convergence issues
f4 <- ~tensor(fu,age,yod,df=c(5,5,5))

# excess hazard model
mod6 <- survPen(f4,data=datCancer,t1=fu,event=dead,expected=rate)
summary(mod6)

# predictions of the surfaces for ages 50, 60, 70 and 80
new.year <- seq(1990,2010,length=30)
new.time <- seq(0,5,length=50)

Z_50 <- outer(new.time,new.year,function(t,y) predict(mod6,data.frame(fu=t,yod=y,age=50))$haz)
Z_60 <- outer(new.time,new.year,function(t,y) predict(mod6,data.frame(fu=t,yod=y,age=60))$haz)
Z_70 <- outer(new.time,new.year,function(t,y) predict(mod6,data.frame(fu=t,yod=y,age=70))$haz)
Z_80 <- outer(new.time,new.year,function(t,y) predict(mod6,data.frame(fu=t,yod=y,age=80))$haz)

# plot the hazard surfaces for a given age
par(mfrow=c(2,2))
persp(new.time,new.year,Z_50,col=colors[facet(Z_50)],main="age 50",theta=20,
  xlab="time since diagnosis",ylab="yod",zlab="excess hazard",ticktype="detailed")
persp(new.time,new.year,Z_60,col=colors[facet(Z_60)],main="age 60",theta=20,
  xlab="time since diagnosis",ylab="yod",zlab="excess hazard",ticktype="detailed")
persp(new.time,new.year,Z_70,col=colors[facet(Z_70)],main="age 70",theta=20,
  xlab="time since diagnosis",ylab="yod",zlab="excess hazard",ticktype="detailed")
persp(new.time,new.year,Z_80,col=colors[facet(Z_80)],main="age 80",theta=20,
survPen.fit

xlab="time since diagnosis",ylab="yod",zlab="excess hazard",ticktype="detailed")
persp(new.time,new.year,Z_80,col=colors[facet(Z_80)],main="age 80",theta=20,
xlab="time since diagnosis",ylab="yod",zlab="excess hazard",ticktype="detailed")

########################################################################

---

survPen.fit

(Excess) hazard model with multidimensional penalized splines for
given smoothing parameters

Description

Fits an (excess) hazard model. If penalized splines are present, the smoothing parameters are specified.

Usage

survPen.fit(
  build,
  data,
  formula,
  max.it.beta = 200,
  beta.ini = NULL,
  detail.beta = FALSE,
  method = "LAML",
  tol.beta = 1e-04
)

Arguments

  build list of objects returned by \texttt{model.cons}
  data an optional data frame containing the variables in the model
  formula formula object specifying the model
  max.it.beta maximum number of iterations to reach convergence in the regression parameters; default is 200
  beta.ini vector of initial regression parameters; default is NULL, in which case the first beta will be \( \log(\text{sum(event)}/\text{sum(t1)}) \) and the others will be zero (except if there are "by" variables in which case all betas are set to zero)
  detail.beta if TRUE, details concerning the optimization process in the regression parameters are displayed; default is FALSE
  method criterion used to select the smoothing parameters. Should be "LAML" or "LCV"; default is "LAML"
  tol.beta convergence tolerance for regression parameters; default is 1e-04. See \texttt{NR.beta} for details

---
Value

Object of class "survPen" (see survPenObject for details)

Examples

library(survPen)

# standard spline of time with 4 knots

data <- data.frame(time=seq(0,5,length=100),event=1,t0=0)

form <- ~ smf(time,knots=c(0,1,3,5))

t1 <- eval(substitute(time), data)
t0 <- eval(substitute(t0), data)
event <- eval(substitute(event), data)

# Setting up the model before fitting
model.c <- model.cons(form,lambda=0,data.spec=data,t1=t1,t1.name="time",
t0=rep(0,100),t0.name="t0",event=event,event.name="event",
expected=NULL,expected.name=NULL,type="overall",n.legendre=20,
cl="survPen(form,data,t1=time,event=event)",beta.ini=NULL)

# fitting
mod <- survPen.fit(model.c,data,form)

<table>
<thead>
<tr>
<th>survPenObject</th>
<th>Fitted survPen object</th>
</tr>
</thead>
</table>

Description

A fitted survPen object returned by function survPen and of class "survPen". Method functions predict and summary are available for this class.

Value

A survPen object has the following elements:

call original survPen call
formula formula object specifying the model
t0.name name of the vector of origin times
t1.name name of the vector of follow-up times
event.name name of the vector of right-censoring indicators
expected.name name of the vector of expected hazard
haz fitted hazard
coefficients: estimated regression parameters. Unpenalized parameters are first, followed by the penalized ones.

type: "net" for net survival estimation with penalized excess hazard model or "overall" for overall survival with penalized hazard model.

df пара: degrees of freedom associated with fully parametric terms (unpenalized).

df smooth: degrees of freedom associated with penalized terms.

p: number of regression parameters.

edf: effective degrees of freedom.

edf1: alternative effective degrees of freedom; used as an upper bound for edf2.

edf2: effective degrees of freedom corrected for smoothing parameter uncertainty.

aic: Akaike information criterion with number of parameters replaced by edf when there are penalized terms. Corresponds to 2*edf - 2*ll.unpen.

aic2: Akaike information criterion corrected for smoothing parameter uncertainty. Be careful though, this is still a work in progress, especially when one of the smoothing parameters tends to infinity.

iter.beta: vector of numbers of iterations needed to estimate the regression parameters for each smoothing parameters trial. It thus contains iter.rho+1 elements.

X: design matrix of the model.

S: penalty matrix of the model.

S.scale: vector of rescaling factors for the penalty matrices.

S.list: Equivalent to pen but with every element multiplied by its associated smoothing parameter.

S.smf: List of penalty matrices associated with all "smf" calls.

S.tensor: List of penalty matrices associated with all "tensor" calls.

S.tint: List of penalty matrices associated with all "tint" calls.

S.rd: List of penalty matrices associated with all "rd" calls.

smooth.name.smf: List of names for the "smf" calls associated with S.smf.

smooth.name.tensor: List of names for the "tensor" calls associated with S.tensor.

smooth.name.tint: List of names for the "tint" calls associated with S.tint.

smooth.name.rd: List of names for the "rd" calls associated with S.rd.

S.pen: List of all the rescaled penalty matrices redimensioned to df.tot size. Every element of S.pen noted S.pen[[i]] is made from a penalty matrix pen[[i]] returned by smooth.cons and is multiplied by S.scale.

grad.unpen.beta: gradient vector of the log-likelihood with respect to the regression parameters.

grad.beta: gradient vector of the penalized log-likelihood with respect to the regression parameters.

Hess.unpen.beta: hessian of the log-likelihood with respect to the regression parameters.
survPenObject

Hess.beta  hessian of the penalized log-likelihood with respect to the regression parameters
Hess.beta.modif  if TRUE, the hessian of the penalized log-likelihood has been perturbed at convergence
ll.unpen  log-likelihood at convergence
ll.pen  penalized log-likelihood at convergence
deriv.rho.beta  transpose of the Jacobian of beta with respect to the log smoothing parameters
deriv.rho.inv.Hess.beta  list containing the derivatives of the inverse of Hess with respect to the log smoothing parameters
deriv.rho.Hess.unpen.beta  list containing the derivatives of Hess.unpen with respect to the log smoothing parameters
lambda  estimated or given smoothing parameters
nb.smooth  number of smoothing parameters
iter.rho  number of iterations needed to estimate the smoothing parameters
optim.rho  identify whether the smoothing parameters were estimated or not; 1 when exiting the function NR.rho; default is NULL
method  criterion used for smoothing parameter estimation
criterion.val  value of the criterion used for smoothing parameter estimation at convergence
LCV  Likelihood cross-validation criterion at convergence
LAML  negative Laplace approximate marginal likelihood at convergence
grad.rho  gradient vector of criterion with respect to the log smoothing parameters
Hess.rho  hessian matrix of criterion with respect to the log smoothing parameters
inv.Hess.rho  inverse of Hess.rho
Hess.rho.modif  if TRUE, the hessian of LCV or LAML has been perturbed at convergence
Ve  Frequentist covariance matrix
Vp  Bayesian covariance matrix
Vc  Bayesian covariance matrix corrected for smoothing parameter uncertainty (see Wood et al. 2016)
Vc.approx  Kass and Steffey approximation of Vc (see Wood et al. 2016)
Z.smf  List of matrices that represents the sum-to-zero constraint to apply for smf splines
Z.tensor  List of matrices that represents the sum-to-zero constraint to apply for tensor splines
Z.tint  List of matrices that represents the sum-to-zero constraint to apply for tint splines
list.smf  List of all smf.smooth.spec objects contained in the model
list.tensor  List of all tensor.smooth.spec objects contained in the model
list.tint  List of all tint.smooth.spec objects contained in the model
list.rd List of all rd.smooth.spec objects contained in the model
U.F Eigen vectors of S.F, useful for the initial reparameterization to separate penalized ad unpenalized subvectors. Allows stable evaluation of the log determinant of S and its derivatives
factor.structure List containing the levels and classes of all factor variables present in the data frame used for fitting
converged convergence indicator, TRUE or FALSE. TRUE if Hess.beta.modif=FALSE and Hess.rho.modif=FALSE (or NULL)

References

Description
Function called recursively inside tensor.prod.X.

Usage
tensor.in(X1, X2)

Arguments
X1 first marginal design matrix with n rows and p1 columns
X2 first marginal design matrix with n rows and p2 columns

Value
Matrix of dimensions n*(p1*p2) representing the row tensor product of the matrices X1 and X2

Examples

library(survPen)

# row-wise tensor product between two design matrices
set.seed(15)
X1 <- matrix(rnorm(10*3),nrow=10,ncol=3)
X2 <- matrix(rnorm(10*2),nrow=10,ncol=2)
tensor.in(X1,X2)
Description

Computes the penalty matrices of a tensor product smooth from the marginal penalty matrices. The code is from function `tensor.prod.penalties` in `mgcv` package.

Usage

tensor.prod.S(S)

Arguments

S list of m marginal penalty matrices

Value

TS List of the penalty matrices associated with the tensor product smooth

Examples

library(survPen)

# tensor product between three penalty matrices
set.seed(15)

S1 <- matrix(rnorm(3*3),nrow=3,ncol=3)
S2 <- matrix(rnorm(2*2),nrow=2,ncol=2)

S1 <- 0.5*(S1 + t(S1) ) ; S2 <- 0.5*(S2 + t(S2) )
tensor.prod.S(list(S1,S2))

Description

Computes the model matrix of tensor product smooth from the marginal bases.

Usage

tensor.prod.X(X)
Arguments

X list of m design matrices with n rows and p1, p2, ... pm columns respectively

Value

T Matrix of dimensions n*(p1*p2*...*pm) representing the row tensor product of the matrices in X

Examples

library(survPen)

# row-wise tensor product between three design matrices
set.seed(15)

X1 <- matrix(rnorm(10*3),nrow=10,ncol=3)
X2 <- matrix(rnorm(10*2),nrow=10,ncol=2)
X3 <- matrix(rnorm(10*2),nrow=10,ncol=2)

tensor.prod.X(list(X1,X2,X3))
Matrix multiplication between two matrices

**Usage**

Mat1 %mult% Mat2

**Arguments**

- **Mat1**: a matrix.
- **Mat2**: another matrix.

**Value**

prod the product Mat1

Matrix multiplication between a matrix and a vector

**Usage**

Mat %vec% vec

**Arguments**

- **Mat**: a matrix.
- **vec**: a vector.

**Value**

prod the product Mat
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