Fitting functional Cox models in R using mgcv package

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Introduction

This document shows how to fit Additive Functional Cox Model (AFCM) (Cui, Crainiceanu, and Leroux 2020) and Linear Functional Cox Model (LFCM) (Gellar et al. 2015; Kong et al. 2018) using the mgcv package in R. The document has two parts. In the first part we simulate a dataset and fit both models step-by-step. In the second part we show model applications to a real NHANES dataset organized using the `rnhanesdata` (Leroux et al. 2019) package.

```
## load packages
library(mgcv)
library(refund)
```

Part 1: Simulated Dataset

We first simulate a dataset `data_analysis` which consists of:

1. `event`: a binary indicator of the event.
2. `survtime`: time to event (in year unit, for example).
3. `X`: a functional predictor stored in an $N \times S$ matrix. Here N is the number of subjects, S is the number of grid points on the functional domain. Each row contains the functional observations of one subject on S locations.
4. `Z`: other scalar predictors. We only include one scalar predictor in this example.

```
## simulate a dataset
set.seed(2021)
N <- 2000 ## number of subjects
S <- 1000 ## number of functional observations per subject
event <- rbinom(N, 1, 0.3) ## 30% of subjects have events observed
survtime <- runif(N, 0, 10) ## observed time
## transformations on X may be necessary for identifiability in practice
X <- matrix(rnorm(N*S), nrow = N, ncol = S)
X <- fpca.face(X)$Yhat ## smooth each curve using fast sandwich smoother
Z <- rnorm(N, 1, 1) ## a scalar predictor

data_analysis <- data.frame(event, survtime, Z, X = I(X)) ## the simulated dataset
rm(event, survtime, X, Z)

str(data_analysis)
```

```
## 'data.frame':    2000 obs. of  4 variables:
##  $ event   : int  0 1 1 0 0 1 0 0 1 1 ...
##  $ survtime: num  7.9091 6.2296 5.396 1.3632 0.0956 ...
##  $ Z       : num  1.157 1.413 0.622 0.538 -0.266 ...
```

```
##  $ X       : 'AsIs' num [1:2000, 1:1000] 0.068 -0.0205 0.0136 -0.0466 -0.0266 ...
##   ..- attr(*, "dimnames")=List of 2
##   .. ..$ : NULL
##   .. ..$ : NULL
```

One great feature of the mgcv package is that it allows to fit functional regression models using `gam()` function; see Chapter 7.11 of Wood (2017). To use this feature, we specify the covariates and the value of `by` parameter in smooth term functions (`s()`, `te()`, `ti()`) of mgcv as **matrices**. In practice, the function term is replaced by a discrete sum approximation.

$$\int_{\mathcal{S}} \gamma(s)X_i(s)ds \approx \frac{1}{S}\sum_{k=1}^{S}\gamma(s_k)X_i(s_k).$$

We first create two variables related to such numerical approximation.

```
## create variables related to numerical approximation
### lmat: numerical integration
data_analysis$lmat <- I(matrix(1/S, ncol=S, nrow=nrow(data_analysis)))
### tmat: time indices of functional observations, we assume an equally-spaced grid here
data_analysis$tmat <- I(matrix(seq(0, 1, len=S), ncol=S, nrow=nrow(data_analysis), byrow=TRUE))
```

Following the instructions in mgcv, we next fit LFCM and AFCM using the `gam()` function.

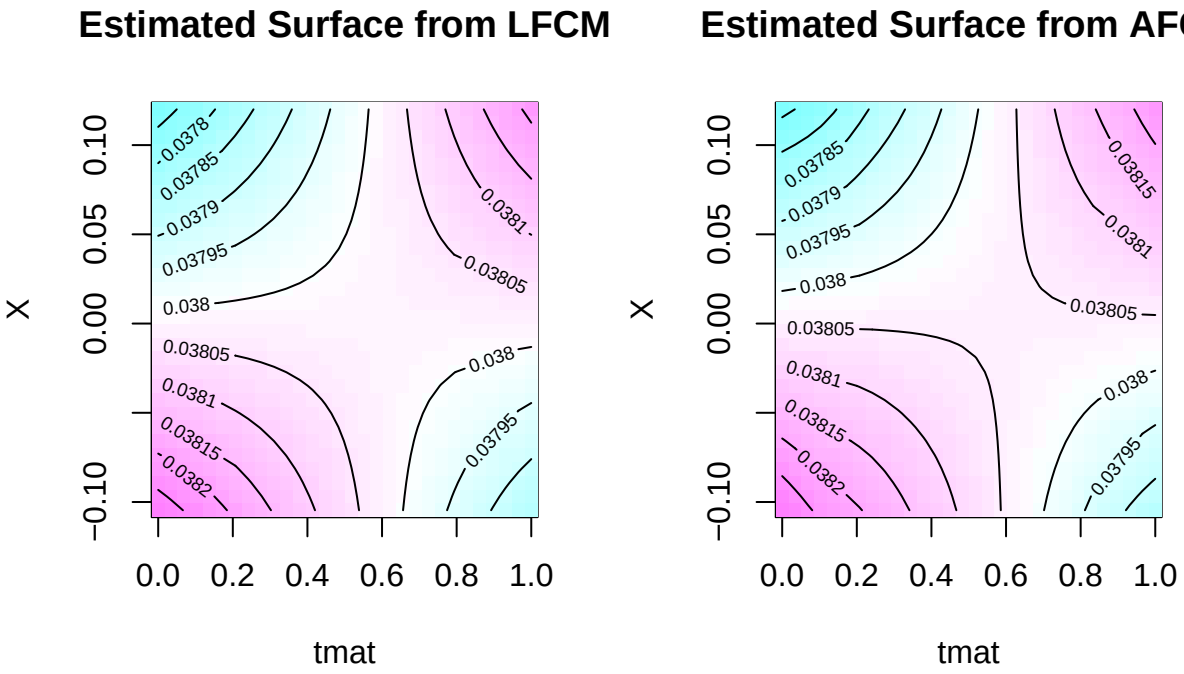
```
## fit LFCM
fit_lfcm <- gam(survtime ~ Z + s(tmat, by=lmat*X, bs="cr", k=10), weights=event,
                data=data_analysis, family=cox.ph())

## fit AFCM
fit_afcm <- gam(survtime ~ Z + ti(tmat, X, by=lmat, bs=c("cr","cr"), k=c(10,10),
                                  mc=c(FALSE,TRUE)), weights=event, data=data_analysis,
                family=cox.ph())
```

To fit a LFCM, we use the univariate smooth function `s()` to specify the linear functional term. Both `tmat` and `lmat*X` are matrices. In this example we use the cubic regression splines (`bs="cr"`) with 10 knots (`k=10`). The time to event variable, `survtime`, is set as the response in the formula, while the event indicator, `event`, is specified as the value of `weights` parameter following mgcv's instructions.

To fit an AFCM, we use the tensor product function `ti()` to specify the bivariate additive term. Different from `te()` function, the `mc` parameter in `ti()` function allows to specify marginal centering constriants. When setting `mc=TRUE` for `X` direction, it exactly matches the additional identifiability constraints for AFCM.

To visualize the estimates, one quick way is to use the `vis.gam()` function from mgcv package.

```
## visualize the estimates
par(mfrow = c(1,2))
vis.gam(fit_lfcm, view = c("tmat", "X"), plot.type = "contour", color = "cm",
        main = "Estimated Surface from LFCM")
vis.gam(fit_afcm, view = c("tmat", "X"), plot.type = "contour", color = "cm",
        main = "Estimated Surface from AFCM")
```



Part 2: NHANES

We now apply LFCM and AFCM to a real NHANES dataset stored in `NHANES.rds`. The detailed inclusion criteria can be found in Cui, Crainiceanu, and Leroux (2020).

```
## load dataset
data_analysis <- readRDS("./NHANES.rds")
dim(data_analysis)
```

```
## [1] 2816   20
```

```
str(data_analysis)
```

```
## 'data.frame':    2816 obs. of  20 variables:
##  $ SEQN           : int  21009 21010 21015 21019 21020 21033 21039 21050 21051 21055 ...
##  $ BMI_cat        : Factor w/ 4 levels "Normal","Underweight",..: 4 3 3 4 1 4 4 3 4 3 ...
##  $ Race           : Factor w/ 5 levels "White","Mexican American",..: 1 1 1 2 4 4 1 1 1 2 ...
##  $ Gender         : Factor w/ 2 levels "Male","Female": 1 2 1 2 2 2 2 1 1 2 ...
##  $ Diabetes       : Factor w/ 2 levels "No","Yes": 1 1 1 1 1 1 1 1 1 1 ...
##  $ CHF            : Factor w/ 2 levels "No","Yes": 1 1 1 2 1 1 1 2 1 1 ...
##  $ CHD            : Factor w/ 2 levels "No","Yes": 1 1 2 2 1 1 1 2 1 1 ...
##  $ Cancer         : Factor w/ 2 levels "No","Yes": 1 1 2 1 1 2 1 1 1 1 ...
##  $ Stroke         : Factor w/ 2 levels "No","Yes": 1 1 1 1 1 1 1 1 1 1 ...
##  $ MobilityProblem: Factor w/ 2 levels "No Difficulty",..: 1 1 2 1 1 1 2 2 1 2 ...
##  $ SmokeCigs      : Factor w/ 3 levels "Never","Former",..: 1 3 2 2 1 1 2 2 2 1 ...
##  $ Age            : num  56 52.8 83.9 50.6 55.6 ...
##  $ Overall_health : Factor w/ 5 levels "Excellent","Very good",..: 2 3 3 3 4 3 2 4 2 3 ...
##  $ PIR            : Factor w/ 3 levels "[0,1)","[1,2.5)",..: 3 2 2 1 2 1 1 2 3 2 ...
##  $ Employed       : Factor w/ 4 levels "Employed: full time",..: 1 3 3 3 1 3 3 3 1 1 ...
##  $ Education      : Factor w/ 3 levels "Less than high school",..: 2 3 3 1 1 2 2 2 2 1 ...
##  $ Alcohol        : Factor w/ 4 levels "Moderate Drinker",..: 2 3 2 2 2 2 2 2 2 2 ...
##  $ time_mort      : num  11.2 12.4 2 12.8 12.8 ...
##  $ event          : int  0 0 1 0 0 0 0 1 0 0 ...
```

```
##  $ act_log_mat    : 'AsIs' num [1:2816, 1:1440] 0 0 0.256 0 0 ...
##   ..- attr(*, "dimnames")=List of 2
##   .. ..$ : chr [1:2816] "21009" "21010" "21015" "21019" ...
##   .. ..$ : chr [1:1440] "1" "2" "3" "4" ...
```

Among all variables, `act_log_mat` stores the minute-level LAC as a 2816×1440 matrix. The event indicator and time-to-event variables are stored in `event` and `time_mort`, respectively.

We first truncate the survival time at 10 years and smooth LAC. The smoothed LAC is our functional predictor $X_i(s)$ in this application.

```
## truncate time to event at 10 years
data_analysis$event[which(data_analysis$time_mort > 10)] <- 0
data_analysis$time_mort[which(data_analysis$time_mort > 10)] <- 10
table(data_analysis$event)
```

```
##
##    0    1
## 2157  659
```

```
## obtain smoothed LAC
data_analysis$act_log_mat_sm   <- I(fpca.face(unclass(data_analysis$act_log_mat))$Yhat)
```

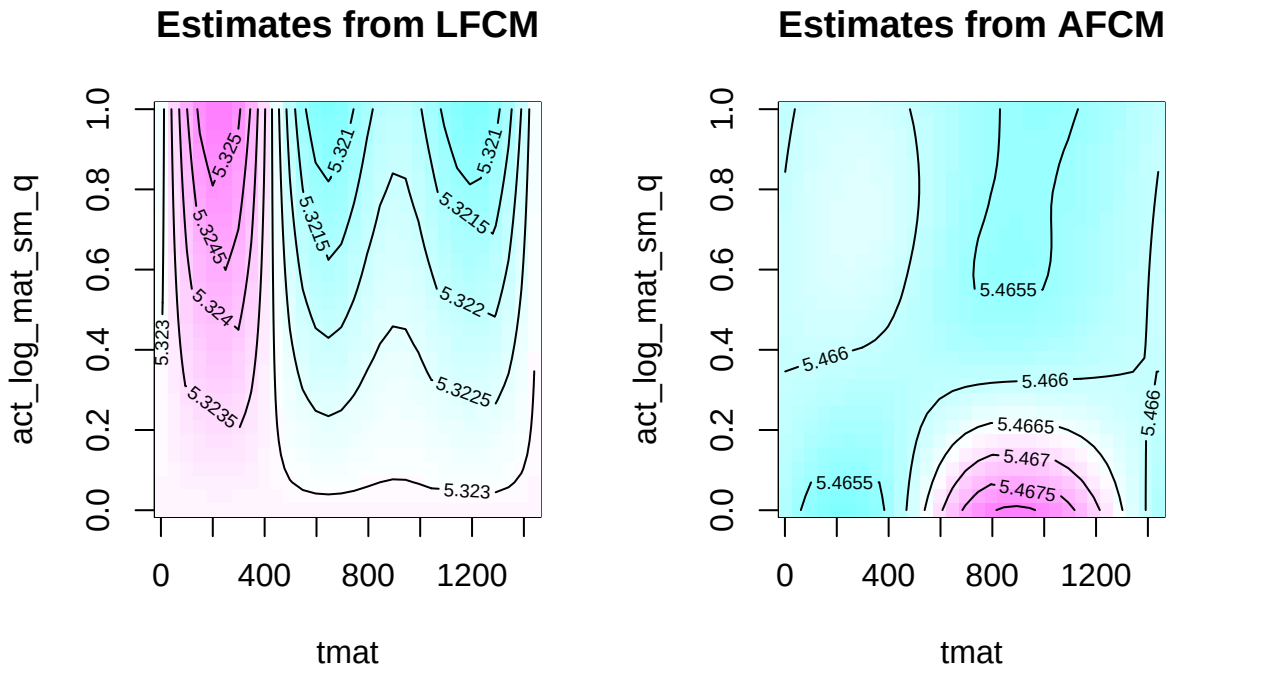
To ensure estimability, we perform quantile transformation on the functional predictor.

```
## obtain quantile-transformed smoothed LAC
data_analysis$act_log_mat_sm_q <- I(apply(data_analysis$act_log_mat_sm, 2,
                                          function(y) ecdf(y)(y)))
```

We next fit LFCM and AFCM on **quantile-transformed** functional predictors using all steps introduced in Part 1. Directly fitting the models using untransformed data will yield uninterpretable patterns, as discussed in Cui, Crainiceanu, and Leroux (2020).

```
### lmat: numerical integration
data_analysis$lmat <- I(matrix(1/1440, ncol=1440, nrow=nrow(data_analysis)))
### tmat: time indices, [0, 1] in our case, but effectively arbitrary
data_analysis$tmat <- I(matrix(1:1440, ncol=1440, nrow=nrow(data_analysis), byrow=TRUE))

## fit LFCM
fit_lfcm <- gam(time_mort ~ Alcohol + Overall_health + PIR + Employed +
                    Age + BMI_cat + SmokeCigs + Race + Education +
                    CHD + Diabetes + CHF + Stroke + MobilityProblem + Cancer +
                    s(tmat, by=lmat*act_log_mat_sm_q, bs="cc", k=10),
                weights=event, data=data_analysis, family=cox.ph())

## fit AFCM
fit_afcm <- gam(time_mort ~ Alcohol + Overall_health + PIR + Employed +
                   Age + BMI_cat + SmokeCigs + Race + Education +
                   CHD + Diabetes + CHF + Stroke + MobilityProblem + Cancer +
                   ti(tmat, act_log_mat_sm_q, by=lmat, bs=c("cc","cr"),
                      k=c(5,5), mc=c(FALSE,TRUE)),
                weights=event, data=data_analysis, family=cox.ph())

## visualize the estimates
par(mfrow = c(1,2))
vis.gam(fit_lfcm, view = c("tmat", "act_log_mat_sm_q"), plot.type = "contour", color = "cm",
        main = "Estimates from LFCM")
vis.gam(fit_afcm, view = c("tmat", "act_log_mat_sm_q"), plot.type = "contour", color = "cm",
```

```
        main = "Estimates from AFCM")
```



References

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Gellar, Jonathan E, Elizabeth Colantuoni, Dale M Needham, and Ciprian M Crainiceanu. 2015. "Cox Regression Models with Functional Covariates for Survival Data." *Statistical Modelling* 15 (3): 256–78.

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