Appendix to the paper:

**Developing clinical prediction models: a step-by-step practical guide with examples in R**

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# **Sample size calculations**

Sample size calculations can be done using the **pmsampsize** package in R1. Here is an example for a continuous outcome.

library(pmsampsize)

pmsampsize(type = "c", rsquared = 0.6, parameters = 10, intercept = 0, sd = 1)

User needs to define the expected , the number of parameters of the models, the expected intercept and standard deviation of the outcome. Additional parameters can be set by hand – see the help file of the package. For a binary outcome we need to provide instead an expected c-statistic of the model, and prevalence of the outcome:

pmsampsize(type = "b", cstatistic = 0.80, parameters = 12,

prevalence = 0.12)

For a time-to-event outcome we can instead use e.g.

pmsampsize(type = "s", rsquared = 0.10, parameters = 15, rate = 0.12,

timepoint = 1, meanfup = 1.25)

As mentioned in our main paper, it is often the case that sample size is fixed. In this case we can use this code to back-calculate the maximum number of parameters (i.e. degrees of freedom) that can be included in the model. Then, we can spend these degrees of freedom to pre-select which predictors, non-linear, or interaction terms to include in the model, given the existing sample size.

# **Example for continuous outcomes**

In this section, we use a simulated example to illustrate some of the steps discussed in the main document, particularly with respect to model development, for the case of a continuous outcome.

## *Simulate a toy example*

The dataset includes:

* five predictors x1, x2, x3, x4, x5, of which x1, x2 are continuous, x3, x4 binary, and x5 categorical.
* the outcome y we want to predict.
* five auxiliary variables z1, z2, z3, z4 and z5.
* a clustering variable clust.

The aim is to build a model using the predictors (x) to predict the outcome (y). The auxiliary variables (z) will only be used for imputation of missing variables and outcomes. Auxiliary variables may be variables that are related to predictors or the outcome, but ones that will not be used for the prediction model. For example, an intermediate outcome cannot be used for predicting y (because its value is not known at time zero, i.e. at baseline), but may still be useful in imputing missing values. The clust variable provides information about an important stratification of the patients in the data. For example, it may be that the data was collected in different centres. This variable will not be used in the model per se but may be useful for imputation and for the internal-external cross-validation process.

rm(list=ls()) # empty memory

set.seed(42) # the answer to life the universe and everything

library(MASS)

N <- 100

Sigma <- outer(1:10, 1:10, function(x,y) 0.5^abs(x-y)) #variance covariance matrix for covariates

x <- mvrnorm(N, rep(0,10), Sigma)

x[,3]<- ifelse(x[,3] > 0.5, 1, 0)

x[,4] <- ifelse(x[,4] > 0, 1, 0)

x[,5] <- cut(x[,5], breaks=c(-Inf, -1, 0, 1, Inf), labels = FALSE)

x[,8] <- ifelse(x[,8] > -0.5, 1, 0)

x[,9] <- ifelse(x[,9] > 0.5, 1, 0)

x[,10] <- cut(x[,10], breaks=c(-Inf, -1, 0, 1, Inf), labels = FALSE)

data.cont.complete <- data.frame(x)

colnames(data.cont.complete) <- c(paste0("x", 1:5), paste0("z", 1:5))

data.cont.complete$y<-with(data.cont.complete, x1+0.2\*x1^2+0.5\*x2-0.2\*x2^2+0.3\*x3+0.2\*x4+

0.2\*(x5==2)-0.1\*(x5==3)+0.4\*(x5==4)+rnorm(N,0,1))

data.cont.complete[,c(3:5, 8:10)] <- lapply(data.cont.complete[,c(3:5, 8:10)], factor)

head(data.cont.complete)

Above we have used the **MASS** package.2 We will now create some missing data and add a clustering variable.

missing.matrix=matrix(0, nrow=nrow(data.cont.complete), ncol=ncol(data.cont.complete))

missing.matrix=matrix(rbinom(length(missing.matrix),1, p=0.1), nrow=nrow(data.cont.complete))

data.cont=data.cont.complete

data.cont[missing.matrix==1]=NA

This is what the data looks like:

head(data.cont)

**x1 x2 x3 x4 x5 z1 z2 z3 z4 z5 y clust**

**4 1.05863018 1.87572000 1 0 2 -1.7989668 -1.9059333 0 0 3 2.3939380 1**

**21 -0.88456382 0.76148109 0 <NA> <NA> 1.3763961 0.9986441 1 1 4 1.1785683 1**

**23 -0.16254908 -0.20319098 0 0 3 NA 0.8798468 0 <NA> 3 0.9866370 1**

**25 -1.55744244 -0.61766584 0 <NA> 1 NA -1.3144854 0 0 4 -1.9483904 1**

**26 0.07578796 -0.07518767 0 0 2 1.5922787 0.3666538 1 0 2 0.6266513 1**

**30 1.27672866 NA 0 1 3 -0.6970741 -0.3550338 1 1 3 0.9573074 1**

This is the distribution of the observed outcomes, using **ggplot2**:3

library(ggplot2)

ggplot(data.cont, aes(x=y)) + geom\_histogram(color="black", fill="white", binwidth = 0.5)

Chart, histogram

Description automatically generated

## *Perform multiple imputations*

We will use the areg.impute function from the **Hmisc** package.4 Since our prediction models will include splines for x1 and x2, we need to include splines in the imputation model.

library(Hmisc)

n.impute <- 10

a <- aregImpute(data=data.cont, I(y)~x1+x2+I(x3)+I(x4)+I(x5)+

z1+z2+I(z3)+I(z4)+I(z5)+clust, n.impute=n.impute, nk=3, match='closest')

# get imputed datasets

imputed1 <- list()

for (i in 1:n.impute){

imputed1[[i]] <- impute.transcan(a, imputation=i, data=data.cont, list.out=TRUE, pr=FALSE, check=FALSE)}

## *Fit the competing prediction models*

Now that we have created the imputed datasets, we can fit our models. Let us start with a ordinary least squares regression model with splines for the two continuous predictors, x1 and x2. Note that since the imputation method used auxiliary variables to impute the outcome, it makes sense to use patients with imputed outcomes when building the model. We use the ols function from **rms**.5

library(rms)

regression.splines<-list()

for (i in 1:n.impute){regression.splines[[i]]<- ols(y~rcs(x1,3)+rcs(x2,3)+x3+x4+x5,data=imputed1[[i]])}

Let us plot6 the fitted splines, to get a sense about their shape:

library(gridExtra)

p.sp1<-ggplot(data.frame(x1=seq(-3,3, 0.1),

y=Predict(regression.splines[[i]], x1=seq(-3,3, 0.1), x2=0, x3=1, x4=1, x5=2)$yhat), aes(x=x1, y=y)) + geom\_smooth()

p.sp2<-ggplot(data.frame(x2=seq(-3,3, 0.1),

y=Predict(regression.splines[[i]], x1=1, x2=seq(-3,3, 0.1), x3=1, x4=1, x5=2)$yhat), aes(x=x2, y=y)) + geom\_smooth()

grid.arrange(p.sp1, p.sp2, ncol=2)

Chart, line chart

Description automatically generated

We have fit a separate prediction model in each of the imputed dataset. To obtain a single prediction for a new patient, we can either:

1. Use Rubin’s rules to pool the coefficients of the prediction models; or
2. Use the models to make separate predictions and average these predictions in the end.

Approach ii. is easier to use, particularly with complicated models with many predictors (e.g. machine learning methods), or when the model has different structure in each imputed dataset (e.g. when it includes variable selection). In what follows we will use this second method. We will define a function for making predictions for a dataframe of new patients.

prediction.ols <- function(new.patient, single.fit = NULL, multiple.fit = NULL){

if(!is.null(multiple.fit)){

mygrid <- expand.grid(k = 1:dim(new.patient)[1], i = 1:length(multiple.fit))

ff <- function(k,i){

with(new.patient, Predict(multiple.fit[[i]], x1= x1[k], x2 = x2[k], x3= x3[k], x4= x4[k], x5= x5[k])$y)

}

prediction\_matrix <- matrix(mapply(ff, mygrid$k, mygrid$i),

nrow = dim(new.patient)[1], ncol = length(multiple.fit))

prediction <- apply(prediction\_matrix, 1, mean)

} else if(!is.null(single.fit)){

ff <- function(k){

with(new.patient, Predict(single.fit, x1= x1[k], x2 = x2[k], x3= x3[k], x4= x4[k], x5= x5[k])$y)

}

prediction <- sapply(1:dim(new.patient)[1], ff)

}

return(prediction)

}

Let us now use the model to predict for a new patient.

new.patient<-data.frame(x1=1.2, x2=-1.6, x3=0, x4=1, x5=4)

**[1] 0.6871744**

Let us also use the model to make predictions for patients in the dataset and compare with observations. We will only use patients with complete observations on the five predictors and the outcome.

complete.data <- data.cont[complete.cases(data.cont[,c(1:5,11)]),]

predicted.ols <- prediction.ols(complete.data, multiple.fit = regression.splines) # these are patients with fully observed data

ggplot(data.frame(observed=complete.data$y, predicted.ols=predicted.ols),

aes(x=predicted.ols, y=observed)) +

geom\_point(size=1) +

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5) +

xlim(-3,3) + ylim(-3,3)+geom\_smooth(method=lm)

Chart, scatter chart

Description automatically generated

Here we see that the model is well calibrated on average. Let us now fit a generalized additive model (GAM). This model allows for a non-linear relationship between the continuous predictor and the outcome, while utilizing penalization (shrinkage). We will use the **mgcv** package.7

library(mgcv)

fit.gam=list()

for(i in 1:n.impute){fit.gam[[i]] <- gam(y ~ x3 + x4 + x5 + s(x1) + s(x2), data = imputed1[[i]])}

We can now use the fitted models to make predictions

prediction.gam <- function(new.patient, single.fit = NULL, multiple.fit = NULL){

if(!is.null(multiple.fit)){

mygrid <- expand.grid(k = 1:dim(new.patient)[1],i = 1:length(multiple.fit))

ff <- function(k,i){

predict.gam(multiple.fit[[i]], newdata = new.patient[k,])}

prediction\_matrix <- matrix(mapply(ff, mygrid$k, mygrid$i),

nrow = dim(new.patient)[1], ncol = length(multiple.fit))

prediction <- apply(prediction\_matrix, 1, mean)

} else if(!is.null(single.fit)){

ff <- function(k){

predict.gam(single.fit, newdata = new.patient[k,])

}

prediction <- sapply(1:dim(new.patient)[1], ff) }

return(prediction) }

prediction.gam(new.patient, multiple.fit = fit.gam)

**[1] 0.8556169**

We can visualize the GAMs

new1 <- data.frame(x1=seq(-3,3, 0.2), x2=0, x3=1, x4=1, x5=2)

p.g1 <- ggplot(data.frame(x1=seq(-3,3, 0.2),

y=prediction.gam(new1, multiple.fit = fit.gam)), aes(x=x1, y=y)) +

geom\_smooth()

new2 <- data.frame(x1=2, x2=seq(-3,3, 0.2), x3=1, x4=1, x5=2)

p.g2 <- ggplot(data.frame(x2=seq(-3,3, 0.2),

y=prediction.gam(new2, multiple.fit = fit.gam)), aes(x=x2, y=y)) +

geom\_smooth()

grid.arrange(p.g1, p.g2, ncol=2)

ggplot(data.frame(observed=complete.data$y,

predicted.gam=predicted.gam),

aes(x=predicted.gam, y=observed)) + geom\_point(size=1) +

geom\_abline(intercept = 0, slope = 1, color="black", linetype="dashed", size=0.5) +

xlim(-5,5) + ylim(-5,5)

Chart, line chart

Description automatically generated

We can make predictions for patients in the dataset with complete predictors and compare with observed outcomes

predicted.gam <- prediction.gam(complete.data, multiple.fit = fit.gam)

ggplot(data.frame(observed=complete.data$y,

predicted.gam=predicted.gam),

aes(x=predicted.gam, y=observed)) + geom\_point(size=1) +

geom\_abline(intercept = 0, slope = 1, color="black", linetype="dashed", size=0.5) +

xlim(-3,3) + ylim(-3,3)+geom\_smooth(method=lm)

Chart, scatter chart

Description automatically generated

Let us also fit a third model, a ridge regression model using the packages **glmnet** and **splines2**.8,9

library(splines2)

library(glmnet)

lambdas <- 10^seq(2, -10, by = -0.3)

#first find the position of the knots for the splines

bsMat.x1 <- bSpline(data.cont$x1[complete.cases(data.cont$x1)],

knots = quantile(data.cont$x1, c(0.25, 0.5, 0.75), na.rm = TRUE))

bsMat.x2 <- bSpline(data.cont$x2[complete.cases(data.cont$x2)],

knots = quantile(data.cont$x2, c(0.25, 0.5, 0.75), na.rm = TRUE))

fit.ridge <- list()

for( i in 1:n.impute){

dfSplined.x1 <- as.data.frame(predict(bsMat.x1, imputed1[[i]]$x1))

dfSplined.x2 <- as.data.frame(predict(bsMat.x2, imputed1[[i]]$x2))

imp <- imputed1[[i]]

imp <- cbind(imp$y, imp$x3, imp$x4, imp$x5, dfSplined.x1, dfSplined.x2)

colnames(imp) <- c("y", "x3", "x4", "x5", paste0("V", as.character(1:(length(colnames(imp))-4))))

data\_glmnet <- model.matrix(y ~., data = imp)

X <- as.matrix(data\_glmnet[,-1])

colnames(X)[1:2] <- c("x3", "x4")

Y <- imp$y

cvfit <- cv.glmnet(X,Y,family = "gaussian", alpha=0,

lambda = lambdas, nfolds=10)

lambda.min <- cvfit$lambda.min

fit.ridge[[i]] <- glmnet(X,Y,family = "gaussian", alpha=0, lambda = lambda.min)

}

Now use the fitted models to make predictions

prediction.ridge <- function(new.patient, single.fit = NULL, multiple.fit = NULL){

if(!is.null(multiple.fit)){

mygrid <- expand.grid(k = 1:dim(new.patient)[1],i = 1:length(multiple.fit))

ff <- function(k,i){

dfSplined.x1 <- as.data.frame(predict(bsMat.x1, new.patient$x1[k]))

dfSplined.x2 <- as.data.frame(predict(bsMat.x2, new.patient$x2[k]))

imp <- data.frame(x3=1\*(new.patient$x3[k]==1),x4=1\*(new.patient$x4[k]==1),x52=1\*(new.patient$x5[k]==2),

x53=1\*(new.patient$x5[k]==3), x54=1\*(new.patient$x5[k]==4), dfSplined.x1,

dfSplined.x2)

colnames(imp)=c("x3","x4","x52","x53","x54", paste0("V", as.character(1:(length(colnames(imp))-5))))

predict(multiple.fit[[i]], newx = as.matrix(imp))

}

prediction\_matrix <- matrix(mapply(ff, mygrid$k, mygrid$i),

nrow = dim(new.patient)[1], ncol = length(multiple.fit))

prediction <- apply(prediction\_matrix, 1, mean)

} else if(!is.null(single.fit)){

ff <- function(k){

dfSplined.x1 <- as.data.frame(predict(bsMat.x1, new.patient$x1[k]))

dfSplined.x2 <- as.data.frame(predict(bsMat.x2, new.patient$x2[k]))

imp <- data.frame(x3=1\*(new.patient$x3[k]==1),x4=1\*(new.patient$x4[k]==1),x52=1\*(new.patient$x5[k]==2),

x53=1\*(new.patient$x5[k]==3), x54=1\*(new.patient$x5[k]==4), dfSplined.x1,

dfSplined.x2)

colnames(imp)=c("x3","x4","x52","x53","x54", paste0("V", as.character(1:(length(colnames(imp))-5))))

predict(single.fit, newx = as.matrix(imp))

}

prediction <- sapply(1:dim(new.patient)[1], ff)

}

return(prediction)

}

prediction.ridge(new.patient, multiple.fit = fit.ridge)

**[1] 0.759369**

predicted.ridge <- prediction.ridge(complete.data, multiple.fit = fit.ridge)

ggplot(data.frame(observed=complete.data$y,

predicted.ridge=predicted.ridge),

aes(x=predicted.ridge, y=observed))+ geom\_point(size=1)+

geom\_abline(intercept = 0, slope = 1, color="black",

linetype="dashed", size=0.5) +

xlim(-3,3) + ylim(-3,3)+geom\_smooth(method=lm)

Chart, scatter chart

Description automatically generated

We can now compare the predictions from the three models

p1<-ggplot(data.frame(predicted.gam=predicted.gam, predicted.ols=predicted.ols),

aes(x=predicted.ols, y=predicted.gam))+ geom\_point(size=1)+

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5)+

xlim(-4.5,4.5)+ylim(-4.5,4.5)

p2<-ggplot(data.frame(predicted.ols=predicted.ols, predicted.ridge=predicted.ridge),

aes(x=predicted.ridge, y=predicted.ols))+ geom\_point(size=1)+

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5)+

xlim(-4.5,4.5)+ylim(-4.5,4.5)

p3<-ggplot(data.frame(predicted.gam=predicted.gam, predicted.ridge=predicted.ridge),

aes(x=predicted.ridge, y=predicted.gam))+ geom\_point(size=1)+

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5)+

xlim(-4.5,4.5)+ylim(-4.5,4.5)

grid.arrange(p1, p2, p3, ncol=3)

Chart, line chart

Description automatically generated

We see similar predictions for the unpenalized splines and the GAM approach, and some small differences with the predictions from ridge.

## *Calculate apparent performance of the models*

After having obtained the predictions from each model and for each patient in the data with fully observed predictors and outcomes, it is easy to assess the models’ performance, by comparing predicted vs. observed outcomes:

calculate\_performance <- function(observed, predicted){

MAE <- mean(abs(observed - predicted)) # mean absolute error

MSE <- mean((observed - predicted)^2) # mean squared error

R2 <- summary(lm(observed~predicted))$r.squared

vec <- c(MAE, MSE, R2)

names(vec) <- c("MAE", "MSE", "R2")

return(vec)

}

apparent.ols <- calculate\_performance(complete.data$y, predicted.ols)

apparent.gam <- calculate\_performance(complete.data$y, predicted.gam)

apparent.ridge <- calculate\_performance(complete.data$y, predicted.ridge)

round(rbind(apparent.ols, apparent.gam, apparent.ridge), digits=2)

**MAE MSE R2**

**apparent.ols 0.82 1.08 0.61**

**apparent.gam 0.78 1.03 0.63**

**apparent.ridge 0.86 1.14 0.61**

As we discuss in the paper, however, this apparent performance may be optimistic.

## *Calculate optimism-corrected performance of the models*

We will use bootstrapping to obtain optimism-corrected assessments of model performance, for our three models. Ideally, we should first bootstrap and then perform the multiple imputations within each bootstrap sample. This, however, would be computationally demanding. Instead, we can bootstrap the already imputed datasets. For each one of the n.impute=10 imputed datasets we create N.bootstrap=10 bootstrap samples. We then fit the models in the bootstrap sample and estimate bootstrap performance. We use the bootstrap models to the imputed dataset and estimate test performance. The difference between the two is optimism. We repeat for all 100 (=n.impute \* N.bootstrap) bootstrap samples. We average, to obtain a final estimate of model optimism. We only focus on mean absolute error (ΜΑΕ), mean squared error (MSE), and coefficient of determination ().

N.bootstrap=10

optimism.ols.eachbootstrap <- optimism.gam.eachbootstrap <- optimism.ridge.eachbootstrap <- matrix(NA, N.bootstrap, 3)

optimism.ols <- optimism.gam <- optimism.ridge <- matrix(NA, n.impute, 3)

for (i in 1:n.impute){

for(j in 1:N.bootstrap){

boot.sample <- sample(length(imputed1[[i]]$y),replace = T)

# create bootstrap sample

imp.boot <- lapply(imputed1[[i]], function(x){x[boot.sample]})

regression.splines.boot <- ols(y~rcs(x1,3)+rcs(x2,3)+x3+x4+x5,data= imp.boot)

fit.gam.boot <- gam(y ~ x3 + x4 + x5 + s(x1) + s(x2), data = imp.boot)

dfSplined.x1 <- as.data.frame(predict(bsMat.x1, imp.boot$x1))

dfSplined.x2 <- as.data.frame(predict(bsMat.x2, imp.boot$x2))

imp <- cbind(imp.boot$y, imp.boot$x3, imp.boot$x4, imp.boot$x5, dfSplined.x1, dfSplined.x2)

colnames(imp)=c("y", "x3", "x4", "x5", paste0("V", as.character(1:(length(colnames(imp))-4))))

data\_glmnet <- model.matrix(y ~ ., data = imp)

X <- as.matrix(data\_glmnet[,-1])

colnames(X)[1:2] <- c("x3", "x4")

Y <- imp$y

cvfit <- cv.glmnet(X,Y,family = "gaussian", alpha=0,

lambda = lambdas, nfolds=10)

lambda.min <- cvfit$lambda.min

fit.ridge.boot <- glmnet(X,Y,family = "gaussian", alpha=0, lambda = lambda.min)

# predict in bootstrap

f1 <- as.data.frame(do.call(cbind, lapply(imp.boot, function(x) {as.numeric(as.character(x))})))

boot.prediction.ols <- prediction.ols(f1, single.fit = regression.splines.boot)

boot.prediction.gam <- prediction.gam(f1, single.fit = fit.gam.boot)

boot.prediction.ridge <- prediction.ridge(f1, single.fit = fit.ridge.boot)

ols.boot <- calculate\_performance(f1$y, boot.prediction.ols)

gam.boot <- calculate\_performance(f1$y, boot.prediction.gam)

ridge.boot <- calculate\_performance(f1$y, boot.prediction.ridge)

# predict in test data

f2 <- as.data.frame(do.call(cbind, lapply(imputed1[[i]], function(x) {as.numeric(as.character(x))})))

test.prediction.ols <- prediction.ols(f2, single.fit = regression.splines.boot)

test.prediction.gam <- prediction.gam(f2, single.fit = fit.gam.boot)

test.prediction.ridge <- prediction.ridge(f2, single.fit = fit.ridge.boot)

ols.test <- calculate\_performance(f2$y, test.prediction.ols)

gam.test <- calculate\_performance(f2$y, test.prediction.gam)

ridge.test <- calculate\_performance(f2$y, test.prediction.ridge)

optimism.ols.eachbootstrap[j,] <- ols.boot - ols.test

optimism.gam.eachbootstrap[j,] <- gam.boot - gam.test

optimism.ridge.eachbootstrap[j,] <- ridge.boot - ridge.test }

optimism.ols[i,] <- apply(optimism.ols.eachbootstrap, 2, mean)

optimism.gam[i,] <- apply(optimism.gam.eachbootstrap, 2, mean)

optimism.ridge[i,] <- apply(optimism.ridge.eachbootstrap, 2, mean)

print(paste0("imputation done: ", i))}

mean.optimism.ols <- apply(optimism.ols, 2, mean)

mean.optimism.gam <- apply(optimism.gam, 2, mean)

mean.optimism.ridge <- apply(optimism.ridge, 2, mean)

optimism.corrected.ols <- apparent.ols - mean.optimism.ols

optimism.corrected.gam <- apparent.gam - mean.optimism.gam

optimism.corrected.ridge <- apparent.ridge - mean.optimism.ridge

round(rbind(optimism.corrected.ols, optimism.corrected.gam, optimism.corrected.ridge), digits=2)

Optimism-corrected measures of performance:

**MAE MSE R2**

**optimism.corrected.ols 0.92 1.33 0.54**

**optimism.corrected.gam 0.98 1.67 0.44**

**optimism.corrected.ridge 1.02 3.85 0.45**

Least squares regression seems to outperform the other two methods, ridge performed worse.

## *Perform internal-external cross-validation*

Finally, we perform an internal-external cross-validation of the models, using the clustering variable, clust. In a nutshell, we take one cluster out, use the remaining clusters to fit the models, and make predictions for the left-out cluster. We then cycle through all clusters. At the end of the procedure, for each patient with complete data for all predictors, we have a single prediction. This prediction is obtained from models that were fit in patients in all other clusters apart from the one the patient belonged to.

clusters <- unique(data.cont$clust)

N.clust <- length(clusters) # 5 clusters in this example

data.in <- data.leftout <- list()

#create the datasets

for(i in 1:N.clust){

data.in[[i]]<-data.cont[data.cont$clust!=clusters[i],]

data.leftout[[i]]<-data.cont[data.cont$clust==clusters[i],]

complete.index <- complete.cases(data.leftout[[i]][,c(paste0("x", 1:5), "y")])

data.leftout[[i]] <- data.leftout[[i]][complete.index,]

}

#impute the data and fit the model

n.impute <- 10

imputed <- regression.splines.CV <- fit.gam.CV <- fit.ridge.CV <- list()

leftout.prediction.ols <- leftout.prediction.gam <- leftout.prediction.ridge <- list()

leftout.performance.ols <- leftout.performance.gam <- leftout.performance.ridge <- list()

for (i in 1:N.clust){

a <- aregImpute(data=data.in[[i]], I(y)~x1+x2+I(x3)+I(x4)+I(x5), n.impute=n.impute, nk=3, match='closest')

for (j in 1:n.impute){

imputed[[j]] <- impute.transcan(a, imputation=j, data=data.in[[i]], list.out=TRUE,

pr=FALSE, check=FALSE)

regression.splines.CV[[j]]<- ols(y~rcs(x1,3)+rcs(x2,3)+x3+x4+x5,data=imputed[[j]])

fit.gam.CV[[j]] <- gam(y ~ x3+x4+x5+s(x1)+s(x2), data = imputed[[j]])

dfSplined.x1 <- as.data.frame(predict(bsMat.x1, imputed[[j]]$x1))

dfSplined.x2 <- as.data.frame(predict(bsMat.x2, imputed[[j]]$x2))

imp <- cbind(imputed[[j]]$y, imputed[[j]]$x3, imputed[[j]]$x4, imputed[[j]]$x5, dfSplined.x1, dfSplined.x2)

colnames(imp) <- c("y", "x3", "x4", "x5", paste0("V", as.character(1:(length(colnames(imp))-4))))

data\_glmnet <- model.matrix(y ~ ., data = imp)

X <- as.matrix(data\_glmnet[,-1])

colnames(X)[1:2] <- c("x3", "x4")

Y <- imp$y

cvfit <- cv.glmnet(X,Y,family = "gaussian", alpha=0,

lambda = lambdas, nfolds=10)

lambda.min <- cvfit$lambda.min

fit.ridge.CV[[j]] <- glmnet(X,Y,family = "gaussian", alpha=0, lambda = lambda.min)

}

leftout.prediction.ols[[i]] <- prediction.ols(data.leftout[[i]], multiple.fit = regression.splines.CV)

leftout.prediction.gam[[i]] <- prediction.gam(data.leftout[[i]], multiple.fit = fit.gam.CV)

leftout.prediction.ridge[[i]] <- prediction.ridge(data.leftout[[i]], multiple.fit = fit.ridge.CV)

leftout.performance.ols[[i]] <- calculate\_performance(data.leftout[[i]]$y, leftout.prediction.ols[[i]])

leftout.performance.gam[[i]] <- calculate\_performance(data.leftout[[i]]$y, leftout.prediction.gam[[i]])

leftout.performance.ridge[[i]] <- calculate\_performance(data.leftout[[i]]$y, leftout.prediction.ridge[[i]])

}

# performance per cluster

#leftout.performance.ols

#leftout.performance.gam

#leftout.performance.ridge

# performance aggregating all clusters

leftout.prediction.ols <- do.call(c, leftout.prediction.ols)

leftout.prediction.gam <- do.call(c, leftout.prediction.gam)

leftout.prediction.ridge <- do.call(c, leftout.prediction.ridge)

IECV.observed <- do.call(rbind, data.leftout)$y

IECV.cluster <- do.call(rbind, data.leftout)$clust

IECV.ols <- calculate\_performance(IECV.observed, leftout.prediction.ols)

IECV.gam <- calculate\_performance(IECV.observed, leftout.prediction.gam)

IECV.ridge <- calculate\_performance(IECV.observed, leftout.prediction.ridge)

round(rbind(IECV.ols, IECV.gam, IECV.ridge), digits=2)

**MAE MSE R2**

**IECV.ols 0.92 1.43 0.50**

**IECV.gam 0.90 1.43 0.49**

**IECV.ridge 0.96 1.49 0.46**

Let us now plot10 results of the internal-external CV.

p4<-ggplot(IECV,

aes(x=leftout.prediction.ols, y=IECV.observed, color=cluster))+ geom\_point(size=2)+

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5)+

xlim(-4,4)+ylim(-4,4) + theme(legend.position = "none")+

geom\_smooth(method=lm, se=F) +ylab("observed")

p5<-ggplot(IECV,

aes(x=leftout.prediction.gam, y=IECV.observed, color=cluster))+ geom\_point(size=2)+

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5)+

xlim(-4,4)+ylim(-4,4) + theme(legend.position = "none")+

geom\_smooth(method=lm, se=F) +ylab("observed")

p6<-ggplot(IECV,

aes(x=leftout.prediction.ridge, y=IECV.observed, color=cluster))+ geom\_point(size=2)+

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5)+

xlim(-4,4)+ylim(-4,4)+geom\_smooth(method=lm, se=F) +ylab("observed")

library(ggpubr)

ggarrange(p4, p5, p6, ncol=3, common.legend = TRUE, legend="bottom")

Each point represents a patient, colours denote clusters.

Chart, scatter chart

Description automatically generated

We see good calibration overall. Finally, we can look into the cluster-specific performance for a model, e.g. aiming to identify patterns across clusters

per.cluster.ols=matrix(leftout.performance.ols[[1]], nrow=1)

for(i in 2: N.clust){

per.cluster.ols=rbind(per.cluster.ols, matrix(leftout.performance.ols[[i]], nrow=1))}

per.cluster.ols=data.frame(per.cluster.ols)

colnames(per.cluster.ols)=c("MAE", "MSE", "R2")

rownames(per.cluster.ols)=paste("cluster",clusters,":")

round(per.cluster.ols, digits=2)

**MAE MSE R2**

**cluster 1 : 0.94 1.72 0.35**

**cluster 2 : 0.99 1.64 0.50**

**cluster 3 : 1.31 2.17 0.36**

**cluster 4 : 0.97 1.46 0.46**

**cluster 5 : 0.56 0.52 0.82**

# **Example for binary outcomes**

## *Simulate a toy example*

We will follow the methods of Section 2.1 to generate an example dataset. One difference is that here we generate for each patient the log-odds of an event using a linear model of the covariates, and from that we simulate the outcome using a Bernoulli distribution.

remove(list=ls()) # empty memory

set.seed(42) # the answer to life the universe and everything

#useful functions

logit <- function(x){log(x/(1-x))}

expit <- function(x){exp(x)/(1+exp(x))}

## simulate data

library(MASS)

N <- 200

Sigma <- outer(1:10, 1:10, function(x,y) 0.5^abs(x-y)) #variance covariance matrix for covariates

x <- mvrnorm(N, rep(0,10), Sigma)

x[,3] <- ifelse(x[,3] > 0.5, 1, 0)

x[,4] <- ifelse(x[,4] > 0, 1, 0)

x[,5] <- cut(x[,5], breaks=c(-Inf, -1, 0, 1, Inf), labels = FALSE)

x[,8] <- ifelse(x[,8] > 1, 0.5, 0)

x[,9] <- ifelse(x[,9] > 1.5, 1, 0)

x[,10] <- cut(x[,10], breaks=c(-Inf, -1, 0.5, 1, Inf), labels = FALSE)

data.bin.complete <- data.frame(x)

colnames(data.bin.complete) <- c(paste0("x", 1:5), paste0("z", 1:5))

logit.py <- with(data.bin.complete,-2+x1+0.2\*x1^2+

0.3\*x2+0.1\*x2^2+0.2\*(x3==2)+0.2\*(x4==2)+0.2\*(x5==2)- 0.1\*(x5==3)+0.2\*(x5==4)+rnorm(N,0,0.1))

py <- expit(logit.py)

data.bin.complete$y <- rbinom(N,1,py)

data.bin.complete[,c(3:5, 8:10, 11)] <- lapply(data.bin.complete[,c(3:5, 8:10, 11)], factor)

# introduce missing data

missing.matrix=matrix(0, nrow=nrow(data.bin.complete), ncol=ncol(data.bin.complete))

missing.matrix=matrix(rbinom(length(missing.matrix),1, p=0.1), nrow=nrow(data.bin.complete))

data.bin=data.bin.complete

data.bin[missing.matrix==1]=NA

Let us see the number of events in the dataset:

table(data.bin$y)

**0 1**

**137 42**

Obviously the dataset is very small (N=200) and with very few events; in real applications we would probably not use such a dataset to develop a model. However, we use it here for illustration purposes. Next, we create a clustering variable:

#create a clustering variable

data.bin$clust <- factor(sample(1:5, size = N, replace = TRUE, prob = rep(0.2,5)))

data.bin <- data.bin[order(data.cont$clust),]

data.bin <- data.bin[order(data.bin$clust),]

head(data.bin)

**x1 x2 x3 x4 x5 z1 z2 z3 z4 z5 y clust**

**11 -0.6914087 -1.2313564 0 0 1 NA 1.53889813 0 0 1 0 1**

**21 -1.1537552 0.8313891 1 1 1 NA -0.18854078 0 0 2 0 1**

**30 0.9075665 NA 1 1 3 0.3859338 -0.60386017 0 0 2 0 1**

**31 0.5666889 0.4127938 0 0 1 -1.8668800 -0.07871549 0 0 4 0 1**

**32 -0.1716803 0.0967226 0 1 3 -0.3332295 NA 0 0 2 0 1**

**36 0.7355847 0.5791860 <NA> 0 4 0.6506267 0.88753494 0.5 1 2 1 1**

The true probability of an event for a new patient, according to the data generating mechanism:

new.patient <- new.patient <- data.frame(x1=-0.3, x2=-0.5, x3=1, x4=1, x5=2)

new.logit <- with(new.patient,-2 +0.5\*x1+0.1\*x1^2+0.2\*x2-0.05\*x2^2+0.1\*(x3==2)+0.2\*(x4==2)+0.2\*(x5==2)-0.1\*(x5==3)+0.2\*(x5==4)) # this is the true log odds

expit(new.logit)

**[1] 0.1124456**

## *Perform multiple imputations*

We can now perform the multiple imputations using the same code4 as in section 2.2:

library(Hmisc)

n.impute <- 10

a <- aregImpute(data=data.bin, I(y)~x1+x2+I(x3)+I(x4)+I(x5)+z1+z2+z3+z4+z5+clust

n.impute=n.impute, nk=3, match='closest')

# get imputed datasets

imputed1=list()

for (i in 1:n.impute){

imputed1[[i]] <- impute.transcan(a, imputation=i, data=data.bin, list.out=TRUE,pr=FALSE, check=FALSE)}

## *Fit the competing prediction models*

Similar to the example of the continuous outcome, we provide code to fit three models. First, a logistic regression with splines:5

library(rms)

regression.splines<-list()

for (i in 1:n.impute){ regression.splines[[i]]<- lrm(y~rcs(x1,3)+rcs(x2,3)+x3+x4+x5, data=imputed1[[i]]) }

Let us plot the fitted splines

spl1<-ggplot(data.frame(x1=seq(-3,3, 0.1),

logit.py=Predict(regression.splines[[i]], x1=seq(-3,3,0.1), x2=0, x3=1, x4=1, x5=2)$yhat),

aes(x=x1, y=logit.py)) + geom\_smooth()

spl2<-ggplot(data.frame(x2=seq(-3,3, 0.1),

logit.py=Predict(regression.splines[[i]], x1=1, x2=seq(-3,3,0.1), x3=1, x4=1, x5=2)$yhat),

aes(x=x2, y=logit.py)) + geom\_smooth()

library(gridExtra)

grid.arrange(spl1,spl2,ncol=2)

Chart, line chart

Description automatically generated

We can now use the fitted models (one per imputed dataset) to make predictions about new patients.

prediction.lr <- function(new.patient, single.fit = NULL, multiple.fit = NULL){

if(!is.null(multiple.fit)){

mygrid <- expand.grid(k = 1:dim(new.patient)[1],i = 1:length(multiple.fit))

ff <- function(k,i){

with(new.patient, Predict(multiple.fit[[i]], x1= x1[k], x2 = x2[k], x3= x3[k], x4= x4[k], x5= x5[k])$y) }

prediction\_matrix <- matrix(mapply(ff, mygrid$k, mygrid$i),

nrow = dim(new.patient)[1], ncol = length(multiple.fit))

prediction <- apply(prediction\_matrix, 1, mean)

} else if(!is.null(single.fit)){

ff <- function(k){

with(new.patient, Predict(single.fit, x1= x1[k], x2 = x2[k], x3= x3[k], x4= x4[k], x5= x5[k])$y) }

prediction <- sapply(1:dim(new.patient)[1], ff) }

return(prediction)}

The predicted probability of an event for the new patients created above is:

expit(prediction.lr(new.patient, multiple.fit = regression.splines))

**[1] 0.1941315**

i.e. quite far from the true probability given above (0.11). We can also calculate probability of an event for all patients with complete data in our dataset, and show them in a histogram:

complete.data <- data.bin[complete.cases(data.bin[,c("x1","x2","x3","x4","x5","y")]),]

predicted.lr <- prediction.lr(complete.data, multiple.fit = regression.splines) # these are patients with fully observed data

ggplot(data.frame(p=expit(predicted.lr)), aes(x=p)) +

geom\_histogram() + geom\_histogram(color="black", fill="white")

Chart, histogram

Description automatically generated

The second model is a GAM:7

library(mgcv)

fit.gam <- list()

for( i in 1:n.impute){

fit.gam[[i]] <- gam(y~x3+x4+x5+s(x1)+s(x2), data = imputed1[[i]], family=binomial)}

prediction.gam <- function(new.patient, single.fit = NULL, multiple.fit = NULL){

if(!is.null(multiple.fit)){

mygrid <- expand.grid(k = 1:dim(new.patient)[1],i = 1:length(multiple.fit))

ff <- function(k,i){

predict.gam(multiple.fit[[i]], newdata = new.patient[k,])

}

prediction\_matrix <- matrix(mapply(ff, mygrid$k, mygrid$i

nrow = dim(new.patient)[1], ncol = length(multiple.fit))

prediction <- apply(prediction\_matrix, 1, mean)

} else if(!is.null(single.fit)){

ff <- function(k){

predict.gam(single.fit, newdata = new.patient[k,])

}

prediction <- sapply(1:dim(new.patient)[1], ff)

}

return(prediction)

}

Predict in the complete dataset:

predicted.gam <- prediction.gam(complete.data, multiple.fit = fit.gam)

Predict for a new patient:

expit(prediction.gam(new.patient, multiple.fit = fit.gam))

**[1] 0.1928841**

The third model is a ridge regression with only linear associations:

library(glmnet)

lambdas <- 10^seq(2, -10, by = -0.3)

fit.ridge <- list()

for( i in 1:n.impute){

imp <- imputed1[[i]]

imp <- with(imp, data.frame(y, x1, x2, x3, x4, x5))

data\_glmnet <- model.matrix(y ~.,data = imp)

data\_glmnet <- data\_glmnet[,-1]

data\_glmnet <- cbind(y = as.numeric(as.character(imp$y)), data\_glmnet = data\_glmnet)

X <- as.matrix(data\_glmnet[,-1])

colnames(X)[3:4] <- c("x3", "x4")

Y <- data\_glmnet[,1]

cvfit <- cv.glmnet(X,Y,family = "binomial",alpha=0, lambda = lambdas, nfolds=10)

lambda.min <- cvfit$lambda.min

fit.ridge[[i]] <- glmnet(X,Y,family = "binomial",alpha=0, lambda = lambda.min)

}

# predict for new patients

prediction.ridge <- function(new.patient, single.fit = NULL, multiple.fit = NULL){

if(!is.null(multiple.fit)){

mygrid <- expand.grid(k = 1:dim(new.patient)[1],i = 1:length(multiple.fit))

ff <- function(k,i){

imp <- with(new.patient, data.frame(x1[k], x2[k], x3[k], x4[k], x52= x5[k]==2, x53= x5[k]==3, x54 = x5[k]==4))

imp[,3:7] <- lapply(imp[,3:7], as.numeric)

colnames(imp) <- c(paste0("x",1:4), "x52", "x53", "x54")

predict(multiple.fit[[i]], newx = as.matrix(imp))

}

prediction\_matrix <- matrix(mapply(ff, mygrid$k, mygrid$i),

nrow = dim(new.patient)[1], ncol = length(multiple.fit))

prediction <- apply(prediction\_matrix, 1, mean)

} else if(!is.null(single.fit)){

ff <- function(k){

imp <- with(new.patient, data.frame(x1[k], x2[k], x3[k], x4[k], x52= x5[k]==2, x53= x5[k]==3, x54 = x5[k]==4))

imp[,3:7] <- lapply(imp[,3:7], as.numeric)

colnames(imp) <- c(paste0("x",1:4), "x52", "x53", "x54")

predict(single.fit, newx = as.matrix(imp))

}

prediction <- sapply(1:dim(new.patient)[1], ff)

}

return(prediction)

}

Predict in the complete dataset:

predicted.ridge <- prediction.ridge(complete.data, multiple.fit = fit.ridge)

Predict for a new patient:

expit(prediction.ridge(new.patient, multiple.fit = fit.ridge))

**[1] 0.2303426**

Let us now compare the three predictions in the log-odds scale:

axislim1=c(-5,3)

p1<-ggplot(data.frame(predicted.gam=predicted.gam, predicted.lr=predicted.lr),

aes(x=predicted.lr, y=predicted.gam))+ geom\_point(size=1)+

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5)+

xlim(axislim1)+ylim(axislim1)

p2<-ggplot(data.frame(predicted.lr=predicted.lr, predicted.ridge=predicted.ridge),

aes(x=predicted.ridge, y=predicted.lr))+ geom\_point(size=1)+

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5)+

xlim(axislim1)+ylim(axislim1)

p3<-ggplot(data.frame(predicted.gam=predicted.gam, predicted.ridge=predicted.ridge),

aes(x=predicted.ridge, y=predicted.gam))+ geom\_point(size=1)+

geom\_abline(intercept = 0, slope = 1, color="black",linetype="dashed", size=0.5)+

xlim(axislim1)+ylim(axislim1)

grid.arrange(p1, p2, p3, ncol=3)

Chart, scatter chart

Description automatically generated

We see similar predictions for logistic regression and GAM, and important differences with the predictions from ridge (which only included linear terms).

## *Calculate apparent performance of the models*

For binary outcomes we need to assess performance in terms of discrimination and calibration. We will use the **pROC** package.11

library(pROC)

apparent.auc.LR<-auc(complete.data$y~predicted.LR)

apparent.auc.gam<-auc(complete.data$y~predicted.gam)

apparent.auc.ridge<-auc(complete.data$y~predicted.ridge)

#calibration in the large

mean(complete.data$y=="1")

**[1] 0.2095238**

mean(expit(predicted.LR))

**[1] 0.2311552**

mean(expit(predicted.gam))

**[1] 0.2329497**

mean(expit(predicted.ridge))

**[1] 0.3687317**

We see that the mean estimated event rate by ridge is quite off. Next, we fit calibration lines and calculate AUC:

calculate\_performance2 <- function(observed, predicted){

auc <- auc(observed~predicted)

glm.fit <- summary(glm(observed~predicted, family = binomial))

calibration.intercept <- glm.fit$coef[1,1]

calibration.slope <- glm.fit$coef[2,1]

vec <- c(auc, calibration.intercept, calibration.slope)

names(vec) <- c("auc", "calibration intercept", "calibration slope")

return(vec)

}

library(pROC)

apparent.lr <- calculate\_performance2(complete.data$y, predicted.lr)

apparent.gam <- calculate\_performance2(complete.data$y, predicted.gam)

apparent.ridge <- calculate\_performance2(complete.data$y, predicted.ridge)

round(rbind(apparent.lr, apparent.gam, apparent.ridge),2)

**auc calibration intercept calibration slope**

**apparent.lr 0.82 0.05 1.22**

**apparent.gam 0.83 0.08 1.28**

**apparent.ridge 0.80 -0.83 1.49**

We can also assess performance using the val.prob function in **rms**:5

val.prob(y=as.numeric(complete.data$y)-1,p=expit(predicted.LR))

val.prob(y=as.numeric(complete.data$y)-1,p=expit(predicted.gam))

val.prob(y=as.numeric(complete.data$y)-1,p=expit(predicted.ridge))

Here is the plot for the first model, showing that it is relatively well calibrated.

Chart

Description automatically generated

Finally, here is alternative code for obtaining a calibration plot

df.calibration <- data.frame(y = complete.data$y, predicted.lr = expit(predicted.lr))

Ngroups <- 10

d1 <- quantile(df.calibration$predicted.lr, probs = seq(0, 1, 1/Ngroups))

g1<-list()

for (i in 1:Ngroups) {

g1[[i]] <- df.calibration[df.calibration$predicted.lr >= d1[i] & df.calibration$predicted.lr < d1[i+1],]

}

predicted <- observed <- vector(mode = "numeric", length = Ngroups)

for (i in 1:Ngroups) {

predicted[i] <- mean(g1[[i]]$predicted.lr)

observed[i] <- mean(g1[[i]]$y == 1)

}

dat1 <- data.frame(pred = predicted, obs = observed)

ggplot(dat1,aes(x=pred,y=obs))+geom\_point(size=3,shape=20)+

labs(x="Predicted from LR", y="Observed") +

geom\_abline(intercept=0,slope=1,color="black",linetype="dashed",size=0.7) + geom\_smooth(method="lm",colour="blue",size=0.7) + theme(aspect.ratio=1)

Chart, scatter chart

Description automatically generated

## *Calculate optimism-corrected performance of the models*

We will use bootstrapping to obtain an optimism-corrected assessment of model performance, as we did in Section 2.5:

# Internal CV via bootstrapping -------------------

# bootstrap in each multiply imputed dataset

N.bootstrap <- 10

optimism.lr.eachbootstrap <- optimism.gam.eachbootstrap <- optimism.ridge.eachbootstrap <- matrix(NA, N.bootstrap, 3)

optimism.lr <- optimism.gam <- optimism.ridge <- matrix(NA, n.impute, 3)

for (i in 1:n.impute){

for(j in 1:N.bootstrap){

boot.sample <- sample(length(imputed1[[i]]$y),replace = T)

# create bootstrap sample

imp.boot <- lapply(imputed1[[i]], function(x){x[boot.sample]})

# fit spline model in bootstrap sample

regression.splines.boot<- lrm(y~rcs(x1,3)+rcs(x2,3)+x3+x4+x5,data=imp.boot)

# fit gam model in bootstrap sample

fit.gam.boot <- gam(y~x3+x4+x5+s(x1)+s(x2), data = imp.boot, family = binomial)

# fit ridge model in bootstrap sample

imp <- imp.boot

imp <- with(imp, data.frame(y, x1, x2, x3, x4, x5))

data\_glmnet <- model.matrix(y ~.,data = imp)

data\_glmnet <- data\_glmnet[,-1]

data\_glmnet <- cbind(y = as.numeric(as.character(imp$y)), data\_glmnet = data\_glmnet)

X <- as.matrix(data\_glmnet[,-1])

colnames(X)[3:4] <- c("x3", "x4")

Y <- data\_glmnet[,1]

cvfit <- cv.glmnet(X,Y,family = "binomial",alpha=0,

lambda = lambdas, nfolds=10)

lambda.min <- cvfit$lambda.min

fit.ridge.boot <- glmnet(X,Y,family = "binomial", alpha=0, lambda = lambda.min)

# predict in bootstrap

f1 <- as.data.frame(do.call(cbind, lapply(imp.boot, function(x) {as.numeric(as.character(x))})))

boot.prediction.lr <- prediction.lr(f1, single.fit = regression.splines.boot)

boot.prediction.gam <- prediction.gam(f1, single.fit = fit.gam.boot)

boot.prediction.ridge <- prediction.ridge(f1, single.fit = fit.ridge.boot)

lr.boot <- calculate\_performance2(f1$y, boot.prediction.lr)

gam.boot <- calculate\_performance2(f1$y, boot.prediction.gam)

ridge.boot <- calculate\_performance2(f1$y, boot.prediction.ridge)

# predict in test data

f2 <- as.data.frame(do.call(cbind, lapply(imputed1[[i]], function(x) {as.numeric(as.character(x))})))

test.prediction.lr <- prediction.lr(f2, single.fit = regression.splines.boot)

test.prediction.gam <- prediction.gam(f2, single.fit = fit.gam.boot)

test.prediction.ridge <- prediction.ridge(f2, single.fit = fit.ridge.boot)

lr.test <- calculate\_performance2(f2$y, test.prediction.lr)

gam.test <- calculate\_performance2(f2$y, test.prediction.gam)

ridge.test <- calculate\_performance2(f2$y, test.prediction.ridge)

optimism.lr.eachbootstrap[j,] <- lr.boot - lr.test

optimism.gam.eachbootstrap[j,] <- gam.boot - gam.test

optimism.ridge.eachbootstrap[j,] <- ridge.boot - ridge.test

}

optimism.lr[i,] <- apply(optimism.lr.eachbootstrap, 2, mean)

optimism.gam[i,] <- apply(optimism.gam.eachbootstrap, 2, mean)

optimism.ridge[i,] <- apply(optimism.ridge.eachbootstrap, 2, mean)

print(paste0("imputation done: ", i))

}

mean.optimism.lr <- apply(optimism.lr, 2, mean)

mean.optimism.gam <- apply(optimism.gam, 2, mean)

mean.optimism.ridge <- apply(optimism.ridge, 2, mean)

optimism.corrected.lr <- apparent.lr - mean.optimism.lr

optimism.corrected.gam <- apparent.gam - mean.optimism.gam

optimism.corrected.ridge <- apparent.ridge - mean.optimism.ridge

round(rbind(optimism.corrected.lr, optimism.corrected.gam, optimism.corrected.ridge),2)

**auc calibration intercept calibration slope**

**optimism.corrected.lr 0.78 -0.17 1.00**

**optimism.corrected.gam 0.75 -0.35 0.82**

**optimism.corrected.ridge 0.76 -1.01 1.30**

Based on these results, the logistic regression with splines model seems to be the best in both calibration and discrimination.

## *Perform internal-external cross-validation*

We follow the procedures of Section 2.6:

# Internal-external CV -------------------

clusters <- unique(data.bin$clust)

N.clust <- length(clusters) # 5 clusters in this example

data.in <- data.leftout <- list()

#create the datasets

for(i in 1:N.clust){

data.in[[i]]<-data.bin[data.bin$clust!=clusters[i],]

data.leftout[[i]]<-data.bin[data.bin$clust==clusters[i],]

complete.index <- complete.cases(data.leftout[[i]][,c(paste0("x", 1:5), "y")])

data.leftout[[i]] <- data.leftout[[i]][complete.index,]

}

n.impute <- 10

imputed <- regression.splines.CV <- fit.gam.CV <- fit.ridge.CV <- list()

leftout.prediction.lr <- leftout.prediction.gam <- leftout.prediction.ridge <- list()

leftout.performance.lr <- leftout.performance.gam <- leftout.performance.ridge <- list()

for (i in 1:N.clust){

a <- aregImpute(data=data.in[[i]], I(y)~x1+x2+I(x3)+I(x4)+I(x5), n.impute=n.impute, nk=3, match='closest')

for (j in 1:n.impute){

imputed[[j]] <- impute.transcan(a, imputation=j, data=data.in[[i]], list.out=TRUE, pr=FALSE, check=FALSE)

regression.splines.CV[[j]]<- lrm(y~rcs(x1,3)+rcs(x2,3)+x3+x4+x5,data=imputed[[j]])

fit.gam.CV[[j]] <- gam(y ~ x3+x4+x5+s(x1)+s(x2), data = imputed[[j]], family = binomial)

imp <- with(imputed[[j]], data.frame(y, x1, x2, x3, x4, x5))

data\_glmnet <- model.matrix(y ~.,data = imp)

data\_glmnet <- data\_glmnet[,-1]

data\_glmnet <- cbind(y = as.numeric(as.character(imp$y)), data\_glmnet = data\_glmnet)

X <- as.matrix(data\_glmnet[,-1])

colnames(X)[3:4] <- c("x3", "x4")

Y <- data\_glmnet[,1]

cvfit <- cv.glmnet(X,Y,family = "binomial",alpha=0,

lambda = lambdas, nfolds=10)

lambda.min <- cvfit$lambda.min

fit.ridge.CV[[j]] <- glmnet(X,Y,family = "binomial", alpha=0, lambda = lambda.min)

}

leftout.prediction.lr[[i]] <- prediction.lr(data.leftout[[i]], multiple.fit = regression.splines.CV)

leftout.prediction.gam[[i]] <- prediction.gam(data.leftout[[i]], multiple.fit = fit.gam.CV)

leftout.prediction.ridge[[i]] <- prediction.ridge(data.leftout[[i]], multiple.fit = fit.ridge.CV)

leftout.performance.lr[[i]] <- calculate\_performance2(data.leftout[[i]]$y, leftout.prediction.lr[[i]])

leftout.performance.gam[[i]] <- calculate\_performance2(data.leftout[[i]]$y, leftout.prediction.gam[[i]])

leftout.performance.ridge[[i]] <- calculate\_performance2(data.leftout[[i]]$y, leftout.prediction.ridge[[i]])

}

#performance per cluster

#leftout.performance.lr

#leftout.performance.gam

#leftout.performance.ridge

# performance aggregating all cluster

leftout.prediction.lr.agg <- do.call(c, leftout.prediction.lr)

leftout.prediction.gam.agg <- do.call(c, leftout.prediction.gam)

leftout.prediction.ridge.agg <- do.call(c, leftout.prediction.ridge)

IECV.observed <- do.call(rbind, data.leftout)$y

IECV.cluster <- do.call(rbind, data.leftout)$clust

IECV.lr <- calculate\_performance2(IECV.observed, leftout.prediction.lr.agg)

IECV.gam <- calculate\_performance2(IECV.observed, leftout.prediction.gam.agg)

IECV.ridge <- calculate\_performance2(IECV.observed, leftout.prediction.ridge.agg)

round(rbind(IECV.lr, IECV.gam, IECV.ridge),2)

**auc calibration intercept calibration slope**

**IECV.lr 0.74 -0.33 0.78**

**IECV.gam 0.75 -0.54 0.62**

**IECV.ridge 0.73 -0.85 1.06**

We can also see the performance of a model when predicting in each of the left-out clusters, to get a sense about the expected heterogeneity of the performance of the prediction model in a new setting:

auc.clusters=data.frame(auc=rep(NA,N.clust), SE=NA, cluster=NA)

for(i in 1:N.clust){

d.cl<-Int.ext.complete[Int.ext.complete$cluster==clusters[i],]

roc1<-roc(d.cl$observed,d.cl$predicted.ridge)

auc.clusters$auc[i]<-auc(roc1)

auc.clusters$SE[i]<-(ci(roc1)[3]-ci(roc1)[1])/3.92

auc.clusters$cluster[i]<-clusters[i]

}

round(auc.clusters,digits=2)

**auc SE cluster**

**1 0.62 0.25 1**

**2 0.88 0.07 2**

**3 0.79 0.13 3**

**4 0.60 0.21 4**

**5 0.72 0.15 5**

Finally we can create a forestplot for AUC using **meta**:12

library(meta)

meta.AUC<-metagen(TE=auc, seTE=SE, studlab = cluster, data=auc.clusters)

forestplot<-forest(meta.AUC, prediction = T, xlim=c(0.4,1),

colgap.left="5mm", rightcols = c("effect", "ci"),

leftlabs = c("Cluster", "AUC", "seTE"))

A picture containing box and whisker chart

Description automatically generated

## *Decision curve analysis*

We perform a decision curve analysis (DCA) using the complete dataset, via the **dcurves** package.13

# plot a decision curve analysis

# see also https://cran.r-project.org/web/packages/dcurves/vignettes/dca.html

library(dcurves)

for.dca=data.frame(obs=as.numeric(complete.data$y)-1,

predicted.gam=expit(predicted.gam),

predicted.lr=expit(predicted.lr), predicted.ridge=expit(predicted.ridge))

for.dca=data.frame(obs=as.numeric(complete.data$y)-1,

predicted.gam=expit(predicted.gam), predicted.ridge=expit(predicted.ridge),

predicted.lr=expit(predicted.lr))

dca1<-dca(obs~predicted.lr+predicted.ridge+predicted.gam, data=for.dca)

plot(dca1, smooth = TRUE)

Chart, line chart

Description automatically generated

We see again that the ridge model is underperforming. We also see that for a threshold probability of ~10% or less, the treat all strategy is equally beneficial to using our models. Of note, the decision curve analysis presented in this section used in-sample predictions (i.e. it may be prone to overfitting). One way to correct for this is again bootstrapping or cross-validation;14,15 however, we do not apply this method here.

# **Example for time-to-event outcomes**

## *Simulate a toy example*

We follow the methods of Section 2.1 to generate an example dataset. Here we will generate 5 covariates x1, x2, x3, x4, x5, and five auxiliary variables z1, z2, z3, z4, z5, a clustering variable clust, the time of follow-up for each patient and the censoring status (0 or 1).

remove(list=ls())

set.seed(42) # the answer to life the universe and everything

# simulate data

library(MASS)

N <- 500

Sigma <- outer(1:10, 1:10, function(x,y) 0.5^abs(x-y)) #variance covariance matrix for covariates

x <- mvrnorm(n = N, rep(0, 10), Sigma)

x[,3] <- ifelse(x[,3] > 0.5, 1, 0) #binary predictor

x[,4] <- ifelse(x[,4] > 0, 1, 0) #binary predictor

x[,5] <- ifelse(x[,5] > 1, 1, 0) #binary predictor

x[,8] <- ifelse(x[,8] > 2, 1, 0) #binary auxiliary variable

x[,9] <- ifelse(x[,9] > 2, 1, 0) #binary auxiliary variable

x[,10] <- cut(x[,10], breaks=c(-Inf, -1, 1, 2, Inf)) #categorical with 4 categories

survdat.compl <- data.frame(x)

colnames(survdat.compl) <- paste0("x", 1:10)

rate <- with(survdat.compl, exp(x1+0.4\*x1^2+0.4\*x2+0.05\*x2^2+(x3==2)+0.5\*(x4==2)-

0.5\*(x5==1)+rnorm(N,0,0.1))/10)

survdat.compl[,c(3:5, 8:10)] <- lapply(survdat.compl[,c(3:5, 8:10)], factor)

fulltime <- rexp(N, rate = rate)

censtimes <- 5 + 20\*runif(N)

mean(censtimes)

survdat.compl$time <- pmin(fulltime, censtimes)

survdat.compl$status <- as.numeric(censtimes > fulltime)

colnames(survdat.compl)[6:10]=c("z1","z2" ,"z3", "z4", "z5")

table(survdat.compl$status)

**0 1**

**137 363**

i.e. 137 patients were censored while 363 experienced the event.

Next, we introduce missing data in the covariates and we create a clustering variable:

# introduce missing data for the covariates

missing.matrix=matrix(0, nrow=nrow(survdat.compl), ncol=10)

missing.matrix=matrix(rbinom(length(missing.matrix),1, p=0.1), nrow=nrow(survdat.compl))

survdat=survdat.compl[,1:10]

survdat[missing.matrix==1]=NA

survdat=cbind(survdat, survdat.compl[11:12])

# create clusters

survdat$clust <- factor(sample(1:5, size = N, replace = TRUE, prob = rep(0.2,5)))

survdat <- survdat[order(survdat$clust),]

head(survdat)

**x1 x2 x3 x4 x5 z1 z2 z3 z4 z5 time status clust**

**10 1.5967150 NA 0 0 <NA> 0.38452856 1.0118199 0 0 2 1.0591365 1 1**

**14 -0.7489477 -0.4119789 0 1 0 -0.04344516 -0.1876478 0 0 2 13.2169852 1 1**

**18 1.7327055 -0.6244390 0 1 1 NA 2.7708399 <NA> 0 <NA> 0.2686032 1 1**

**27 -1.4119981 -0.2056145 0 0 0 1.15318721 0.6450764 0 0 4 16.8137300 0 1**

**29 0.6733386 0.3010077 0 0 <NA> 0.65092121 0.9063692 0 0 1 5.0152636 1 1**

**35 -0.5702342 -0.6440433 0 0 0 -0.51055435 0.3857109 0 0 2 9.8360372 0 1**

## *Visualize data*

Before commencing with the analyses, we can visualize the data, starting with a Kaplan-Meier curve. We use **ggplot2**, **ggfortify**, and **survival** here:3,16,17

# KM curve

library(ggplot2)

library(ggfortify)

library(survival)

model\_fit <- survfit(Surv(time, status) ~ 1, data=survdat)

autoplot(model\_fit) +

labs(x = "\n Survival Time (Days) ", y = "Survival Probabilities \n",

title = "Survival Times") +

theme(plot.title = element\_text(hjust = 0.5),

axis.title.x = element\_text(face="bold", size = 12),

axis.title.y = element\_text(face="bold", size = 12),

legend.title = element\_text(face="bold", size = 10))

Chart, histogram

Description automatically generated

We can also plot for different levels of the covariates, e.g. for different values of x5:

### plot survival curves for specific levels of covariates

model\_fit2 <- survfit(Surv(time, status) ~ x5, data=survdat)

autoplot(model\_fit2) +

labs(x = "\n Survival Time (Days) ", y = "Survival Probabilities \n",

title = "Survival Times") +

theme(plot.title = element\_text(hjust = 0.5),

axis.title.x = element\_text(face="bold", size = 12),

axis.title.y = element\_text(face="bold", size = 12),

legend.title = element\_text(face="bold", size = 10))+ xlim(0,30)

Chart, histogram

Description automatically generated

## *Perform multiple imputations*

The data has several missing entries, so we need to perform multiple imputations. Following White and Royston,18 for the imputation we will use the cumulative baseline hazard estimated by the Nelson–Aalen estimator, in addition to other covariates:

# Impute missing data

library(Hmisc)

n.impute <- 10

survdat$nelsonaalen <- nelsonaalen(survdat, time, status)

a <- aregImpute(data=survdat, ~status+x1+x2+I(x3)+I(x4)+I(x5)+

z1+z2+I(z3)+I(z4)+I(z5)+clust+nelsonaalen, n.impute=n.impute, nk=3, match='closest')

# get imputed datasets

imputed <- list()

for (i in 1:n.impute){

imputed[[i]] <- impute.transcan(a, imputation=i, data=survdat, list.out=TRUE, pr=FALSE, check=FALSE)

imputed[[i]]$time<-survdat$time

}

## *Fit a prediction model*

Having created the imputed dataset, we can now fit a prediction model. We hereby use a Weibull model with smoothing splines for the continuous predictors:

# Weibull model with smoothing splines

fit.model <- list()

for(i in 1:n.impute){

fit.model[[i]] <- survreg(Surv(time, status)~pspline(x1, df=2)+pspline(x2, df=2)+ridge(x3,x4, scale=T),

imputed[[i]], dist="weibul")

}

We can use this model to make predictions for a new patient and draw the expected survival curve.

# predict for new patient

new.patient <- data.frame(x1 = 0.5, x2 = 0.2, x3 = as.factor(1), x4 = as.factor(2))

prediction.weibull.time <- function(new.patient, fit.model = NULL){

pct <- 1:99/100

predicted.exp <- list()

for(i in 1:n.impute){

ptime <- predict(fit.model[[i]], newdata=new.patient, type='quantile', p=pct, se=TRUE)

predicted.exp[[i]] <- data.frame(surv=pct, pred=ptime$fit,var=ptime$se.fit^2)

}

predicted.exp.average <- Reduce("+", predicted.exp) / n.impute

means <- predicted.exp.average[,2]

U <- predicted.exp.average[,3]

errors <- list()

for(i in 1:n.impute){

errors[[i]] <- (predicted.exp[[i]]$pred-means)^2

}

B <- 1/(n.impute-1)\*(Reduce("+", errors))

varMI <- U + (1+1/n.impute)\*B

results <- data.frame("percentiles.surv"=pct,"means"=means, "sd" = sqrt(varMI),

"lowerCI"=means-1.96\*sqrt(varMI), "upperCI"=means+1.96\*sqrt(varMI))

return(results)

}

predictions.time <- prediction.weibull.time(new.patient, fit.model)

ggplot(predictions.time, aes(x = means, y =1 - percentiles.surv )) +

geom\_line(col="black") +

geom\_ribbon(aes(xmin = lowerCI, xmax = upperCI),

alpha=0.1,

linetype="dashed",

color="grey")+xlab("days")+ylab("Survival probability") +xlim(0,30)

Chart, histogram

Description automatically generated

We can also calculate the so-called linear predictor, which we will use in the next sections to assess of model performance:

# calculate the linear predictor

prediction.weibull <- function(new.patient, single.fit = NULL, multiple.fit = NULL){

if(!is.null(multiple.fit)){

ff <- function(i){

predict(multiple.fit[[i]], newdata = new.patient, type = "lp")

}

prediction\_matrix <- sapply(1:length(multiple.fit), ff)

if(dim(new.patient)[1] == 1){

prediction <- mean(prediction\_matrix)

} else{

prediction <- apply(prediction\_matrix, 1, mean)

}

} else if(!is.null(single.fit)){

prediction <- predict(single.fit, newdata = new.patient, type = "lp")

}

return(prediction)

}

complete.data <- survdat[complete.cases(survdat[,1:5]),]

predicted.weibull <- prediction.weibull(complete.data, multiple.fit = fit.model)

## *Calculate apparent performance of the model*

As was the case for the binary outcome, we need to assess both calibration and discrimination of a new model. Discrimination is usually assessed via Harrell’s c-statistic,19 or using the modification proposed by Uno et al.20 Calibration can be estimated by refitting a simple Cox model with the linear predictor of the model as the only covariate:

# Assess apparent performance (no optimism correction) -------------------

calculate\_performance <- function(time = NULL, status = NULL, lp = NULL){

#discrimination

harrell\_C <- concordance(Surv(time, status) ~ lp)

harrell\_C\_est <- harrell\_C$concordance

#harrell\_C\_var <- harrell\_C$var

Uno\_C <- concordance(Surv(time, status) ~ lp, timewt = "n/G2")

Uno\_C\_est <- Uno\_C$concordance

#Uno\_C\_var <- Uno\_C$var

#calibration

second\_model <- survreg(Surv(time, status) ~ lp, dist="weibul")

calslope <- second\_model$coef[2]

returnVec <- c(harrell\_C\_est, Uno\_C\_est, calslope)

names(returnVec) <- c("Harrel\_C", "Uno\_C", "calibration.slope")

return(returnVec)

}

apparent.weibull <- calculate\_performance(time = complete.data$time, status = complete.data$status,lp = predicted.weibull)

round(apparent.weibull,2)

**Harrel\_C Uno\_C calibration.slope**

**0.76 0.75 1.07**

We can also assess calibration at a specific time point by comparing observed vs. predicted events. We use here the code provided by McLernon et al.21, after adapting it for multiply imputed datasets:

# calibration in the large

timepoint <- 5

# Observed

obj <- summary(survfit(

Surv(time, status) ~ 1,

data = complete.data),

times = timepoint)

obs\_t <- 1 - obj$surv

# Predicted risk

prediction.weibull2 <- function(new.patient, fit.model = NULL, time.point = NULL){

if(is.null(time.point)){

pct <- 10\*1:300/100

} else{

pct <- time.point

}

predicted.exp <- list()

for(i in 1:n.impute){

mu\_hat <- predict(fit.model[[i]], newdata = new.patient, type = "lp")

predicted.exp[[i]] <- 1 - pweibull(pct, shape = 1/fit.model[[i]]$scale,

scale = exp(mu\_hat))

}

predicted.exp.average <- Reduce("+", predicted.exp) / n.impute

results <- data.frame(time = pct, means = predicted.exp.average)

return(results)

}

predictions <- list()

for (i in 1:dim(complete.data)[1]){

predictions[[i]] <- prediction.weibull2(complete.data[i,], fit.model, time.point = timepoint)$means

}

est.surv <- unlist(predictions)

pred <- 1 - est.surv

# Expected

exp\_t <- mean(pred)

OE\_t <- obs\_t / exp\_t

alpha <- .05

OE\_summary <- c(

"OE" = OE\_t,

"2.5 %" = OE\_t \* exp(-qnorm(1 - alpha / 2) \* sqrt(1 / obj$n.event)),

"97.5 %" = OE\_t \* exp(+qnorm(1 - alpha / 2) \* sqrt(1 / obj$n.event))

)

round(OE\_summary,2)

**OE 2.5 % 97.5 %**

**1.02 0.87 1.19**

We can inspect calibration graphically:

# drawing a calibration plot

library(rms)

predictions <- list()

for (i in 1:dim(complete.data)[1]){

predictions[[i]] <- prediction.weibull2(complete.data[i,], fit.model, time.point = complete.data[i,]$time)$means

}

est.surv <- unlist(predictions)

f <- val.surv(S= Surv(complete.data$time, complete.data$status),

est.surv = est.surv)

plot(f, xlab="predicted survival", ylab="observed survival")

Chart, line chart

Description automatically generated

We can also assess calibration by checking the observed (i.e. Kaplan Meier) survival with the one estimated by the model.

# drawing calibration plot 2

# calibration plot overall

prediction.weibull2 <- function(new.patient, fit.model = NULL){

pct <- 10\*1:300/100

predicted.exp <- list()

for(i in 1:n.impute){

mu\_hat <- predict(fit.model[[i]], newdata = new.patient, type = "lp")

predicted.exp[[i]] <- 1 - pweibull(pct, shape = 1/fit.model[[i]]$scale,

scale = exp(mu\_hat))

}

predicted.exp.average <- Reduce("+", predicted.exp) / n.impute

results <- data.frame(time = pct, means = predicted.exp.average)

return(results)

}

predictions <- list()

for (i in 1:dim(complete.data)[1]){

predictions[[i]] <- prediction.weibull2(complete.data[i,],fit.model)$means

}

predictions.mean <- apply(do.call(cbind, predictions), 1, mean)

m2 <- survfit(Surv(time, status) ~ 1, data= complete.data)

res <- summary(m2, censored = T)

dt1 <- with(res, data.frame(time = time, surv = surv, upper = upper,

lower = lower))

dt3 <- data.frame(time = c(10\*1:300/100, dt1$time),

surv = c(predictions.mean, dt1$surv),

group = c(rep("pred",300), rep("obs",length(dt1$surv))))

ggplot(data = dt3) +

geom\_line(aes(x = time, y = surv, group = group, colour = group,

linetype = group, size = group)) +

scale\_size\_manual(values = c(0.5,0.1)) +

scale\_color\_manual(values = c("red", "black")) +

scale\_linetype\_manual(values = c("solid", "dashed")) +

xlim(0,30)

Chart, line chart

Description automatically generated

The red line above is the Kaplan Meier estimate, the dotted line is the predicted survival from the model. Additionally, we can plot by levels of covariates, to also assess discrimination.

# calibration plot by levels of covariates

group1 <- complete.data[complete.data$x3 == 0,]

group2 <- complete.data[complete.data$x3 == 1,]

predictions.group1 <- list()

for (i in 1:dim(group1)[1]){

predictions.group1[[i]] <- prediction.weibull2(group1[i,],fit.model)$means

}

predictions.group2 <- list()

for (i in 1:dim(group2)[1]){

predictions.group2[[i]] <- prediction.weibull2(group2[i,],fit.model)$means

}

predictions.mean.group1 <- apply(do.call(cbind, predictions.group1), 1, mean)

predictions.mean.group2 <- apply(do.call(cbind, predictions.group2), 1, mean)

predictions.both.groups <- data.frame(means= c(predictions.mean.group1,predictions.mean.group2),

group= c(rep("x3=1, fitted", 300), rep("x3=2, fitted", 300)), percentiles.surv = 1:300/100)

m2 <- survfit(Surv(time, status) ~ x3, data= complete.data[complete.cases(complete.data[,1:5]),])

res <- summary(m2, censored = T)

dt1 <- with(res, data.frame(time = time, surv = surv, upper = upper,

lower = lower, strata=strata))

dt2 <- data.frame(time = c(10\*1:300/100, 10\*1:300/100, dt1$time),

surv = c(predictions.both.groups$means, dt1$surv),

group = c(predictions.both.groups$group, dt1$strata))

dt2$group[dt2$group == "1"] <- "x3=1, observed"

dt2$group[dt2$group == "2"] <- "x3=2, observed"

ggplot(data = dt2) +

geom\_line(aes(x = time, y = surv, group = group, colour=group, linetype=group,

size = group)) +

scale\_size\_manual(values=c(0.8,0.1,0.8,0.1))+

scale\_color\_manual(values=c("red", "red", "black", "black"))+

scale\_linetype\_manual(values=c("solid", "dashed","solid", "dashed"))+

xlim(0,25)

A picture containing text, racquetball, sport, athletic game

Description automatically generated

## *Calculate optimism-corrected performance of the models*

We will use bootstrapping on the imputed datasets to obtain an optimism-corrected assessment of model performance, as we did in Section 2.5:

# Internal CV via bootstrapping -------------------

# bootstrapping in each multiply imputed dataset

n.bootstrap <- 10

n.impute <- 10

optimism.weibull.eachbootstrap <- matrix(NA, n.bootstrap, 3)

optimism.weibull <- matrix(NA, n.impute, 3)

for (i in 1:n.impute){

for(j in 1:n.bootstrap){

boot.sample <- sample(length(imputed[[i]]$time), replace = T)

# create bootstrap sample

imp.boot <- lapply(imputed[[i]], function(x){x[boot.sample]})

# fit spline model in bootstrap sample

fit.weibull.boot <- survreg(Surv(time, status)~pspline(x1, df=2)+pspline(x2, df=2)+ridge(x3,x4, scale=T),imp.boot, dist="weibul")

# predict in bootstrap

f1 <- as.data.frame(do.call(cbind, lapply(imp.boot, function(x) {as.numeric(as.character(x))})))

boot.prediction.weibull <- prediction.weibull(f1, single.fit = fit.weibull.boot)

weibull.boot <- calculate\_performance(time = f1$time, status = f1$status, lp = boot.prediction.weibull)

# predict in test data

f2 <- as.data.frame(do.call(cbind, lapply(imputed[[i]], function(x) {as.numeric(as.character(x))})))

test.prediction.weibull <- prediction.weibull(f2, single.fit = fit.weibull.boot)

weibull.test <- calculate\_performance(time = f2$time, status = f2$status, lp = test.prediction.weibull)

optimism.weibull.eachbootstrap[j,] <- weibull.boot - weibull.test

}

optimism.weibull[i,] <- apply(optimism.weibull.eachbootstrap, 2, mean)

print(paste0("imputation done: ", i))

}

mean.optimism.weibull <- apply(optimism.weibull, 2, mean)

optimism.corrected.weibull <- apparent.weibull - mean.optimism.weibull

optimism.corrected.weibull

**Harrel\_C Uno\_C calibration.slope**

**0.76 0.75 1.06**

Essentially we see no optimism here. This was expected since the dataset is large, there were many events, and the model had few parameters.

## *Perform internal-external cross-validation*

We perform an internal-external cross-validation using the clust variable, as in Section 2.6:

# Internal-external CV -------------------

clusters <- unique(survdat$clust)

N.clust <- length(clusters) # 5 clusters in this example

data.in <- data.leftout <- list()

#create the datasets

for(i in 1:N.clust){

data.in[[i]]<- survdat[survdat$clust!=clusters[i],]

data.leftout[[i]]<- survdat[survdat$clust==clusters[i],]

complete.index <- complete.cases(data.leftout[[i]][,c(paste0("x", 1:5))])

data.leftout[[i]] <- data.leftout[[i]][complete.index,]

}

n.impute <- 10

imputed <- fit.weibull.CV <- list()

leftout.prediction.weibull <- leftout.performance.weibull <- list()

for (i in 1:N.clust){

data.in[[i]]$nelsonaalen <- nelsonaalen(data.in[[i]], time, status)

meth <- make.method(data.in[[i]])

pred <- make.predictorMatrix(data.in[[i]])

pred[,"time"] <- 0 # don't include time variable in the imputation;instead we have baseline hazard

imp.surv <- mice(data.in[[i]], m = n.impute)

imputed <- list()

impc <- complete(imp.surv, action="long")

for(j in 1:n.impute){

imputed[[j]] <- impc[impc$.imp==j, c(3:7, 13:15)]

}

for (j in 1:n.impute){

fit.weibull.CV[[j]] <- survreg(Surv(time, status)~pspline(x1, df=2)+pspline(x2, df=2)+ridge(x3,x4, scale=T),

imputed[[j]], dist="weibul")

}

leftout.prediction.weibull[[i]] <- prediction.weibull(data.leftout[[i]], multiple.fit = fit.weibull.CV)

leftout.performance.weibull[[i]] <- calculate\_performance(time = data.leftout[[i]]$time, status = data.leftout[[i]]$status,

lp = leftout.prediction.weibull[[i]])

}

# performance per cluster

IECV.weibull=data.frame(t(leftout.performance.weibull[[1]]))

for( i in 2:N.clust){IECV.weibull=rbind(IECV.weibull, t(leftout.performance.weibull[[i]]))}

IECV.weibull$cluster=1:N.clust

round(IECV.weibull,2)

**Harrel\_C Uno\_C calibration.slope cluster**

**1 0.75 0.74 1.22 1**

**2 0.79 0.78 1.28 2**

**3 0.73 0.74 0.83 3**

**4 0.78 0.77 1.08 4**

**5 0.73 0.70 0.98 5**

## *Decision curve analysis*

We will use the complete dataset for this analysis. First, we need to set a time point of interest. Then we need to use the models developed in the imputed datasets to predict the probability of an event at this time point, for each patient in the complete dataset.

### decision curve analysis -----

library(dcurves)

timepoint<-10

ptime <- predict(fit.model[[i]], newdata=complete.data, type='quantile', p=10, se=TRUE)

pred.complete=matrix(0, nrow=dim(complete.data)[1], ncol=n.impute)

for(i in 1:n.impute){

mu\_hat <- predict(fit.model[[i]], newdata = complete.data, type = "lp")

pred.complete[,i]= pweibull(timepoint, shape = 1/fit.model[[i]]$scale,

scale = exp(mu\_hat))}

pred.complete2=rowMeans(pred.complete)

for.dca=data.frame(time=complete.data$time, status=complete.data$status, pred=pred.complete2)

dca1<-dca(Surv(time, status) ~ pred,

data = for.dca,thresholds = 1:80 / 100,

time = timepoint)

plot(dca1,smooth = TRUE)

Chart, line chart

Description automatically generated

We see that the model is only useful for a threshold probability of around 40% or more. See also the note in Section 3.7 about overfitting.

# **Example for competing risks outcomes**

Here we will reuse code provided by van Geloven et al.22 after adjusting it for multiple imputations.

## *Simulate a toy example*

We will first simulate a toy example, assuming there are 2 competing events. We will generate again 10 covariates (5 predictors, 5 auxiliary variables) x1, x2, x3, x4, x5, z1, z2, z3, z4, z5, a clustering variable clust, the time of follow-up for each patient and the type of an event, i.e. status, which can be 0 (for patients that did not have an event by the end of their longest follow-up), 1, and 2 (for patients having event type 1 or 2 respectively).

# parts of the code copied from https://github.com/survival-lumc/ValidationCompRisks/blob/main/Prediction\_CSC\_minimal.R

# Original paper https://www.bmj.com/content/bmj/377/bmj-2021-069249.full.pdf

remove(list=ls())

set.seed(42) # the answer to life the universe and everything

## simulate data ------------

library(MASS)

N <- 500

Sigma <- outer(1:10, 1:10, function(x,y) 0.5^abs(x-y)) #variance covariance matrix for covariates

x <- mvrnorm(n = N, rep(0, 10), Sigma)

x[,3] <- ifelse(x[,3] > 0.5, 1, 0) #binary predictor

x[,4] <- ifelse(x[,4] > 0, 1, 0) #binary predictor

x[,5] <- ifelse(x[,5] > 1, 1, 0) #binary predictor

x[,8] <- ifelse(x[,8] > 2, 1, 0) #binary auxiliary variable

x[,9] <- ifelse(x[,9] > 2, 1, 0) #binary auxiliary variable

x[,10] <- cut(x[,10], breaks=c(-Inf, -1, 1, 2, Inf)) #categorical with 4 categories

survdat.compl <- data.frame(x)

colnames(survdat.compl) <- paste0("x", 1:10)

rate1 <- with(survdat.compl, exp(-0.5+x1+0.4\*x2+(x3==2)+0.5\*(x4==2)+0.5\*(x5==1)+rnorm(N,0,0.1))/10)

rate2 <- with(survdat.compl, exp(-1+0.1\*x1+0.2\*x2+(x3==2)+0.1\*(x4==2)-0.2\*(x5==1)+rnorm(N,0,0.1))/10)

survdat.compl[,c(3:5, 8:10)] <- lapply(survdat.compl[,c(3:5, 8:10)], factor)

fulltime <- rexp(N, rate = rate1)

fulltime2 <- rexp(N, rate = rate2)

censtimes <- 10 + 20\*runif(N)

mintime <- pmin(fulltime, fulltime2, censtimes)

survdat.compl$time <- mintime

survdat.compl$status <- 0

survdat.compl$status[mintime == fulltime] <- 1

survdat.compl$status[mintime == fulltime2] <- 2

# introduce missing data for the covariates

missing.matrix=matrix(0, nrow=nrow(survdat.compl), ncol=10)

missing.matrix=matrix(rbinom(length(missing.matrix),1, p=0.02), nrow=nrow(survdat.compl))

survdat=survdat.compl[,1:10]

survdat[missing.matrix==1]=NA

survdat=cbind(survdat, survdat.compl[11:12])

#create clusters

survdat$clust <- factor(sample(1:5, size = N, replace = TRUE, prob = rep(0.2,5)))

survdat <- survdat[order(survdat$clust),]

#inspect data

head(survdat)

**x1 x2 x3 x4 x5 x6 x7 x8 x9 x10 time status clust**

**5 -1.7484193 0.18934122 <NA> 0 0 0.5400806 0.7311373 0 0 1 6.753887 2 1**

**7 -1.4796022 -1.30521258 0 0 0 -0.9412580 -1.0006861 0 0 2 19.014273 0 1**

**8 -1.4005888 -1.91554654 0 1 0 1.2988185 2.7307122 0 0 1 9.667323 1 1**

**10 1.5967150 1.47832616 0 0 0 0.3845286 1.0118199 0 <NA> 2 2.631073 1 1**

**11 -0.4144015 0.05737876 0 1 0 -2.0569517 -1.2557112 0 0 1 5.351348 2 1**

**12 -1.7079157 -1.26334587 0 0 0 -0.9881902 -2.2165987 0 0 2 23.622897 0 1**

table(survdat$status)

**0 1 2**

**106 267 127**

As we see, 106 of the patients did not have any event, 267 had event type 1, and 127 had event type 2.

## *Perform multiple imputations*

We now use all predictors and auxiliary variables, status and log-time to perform the imputations. Here we use **mice**:23

# Impute missing data --------------

library(mice)

n.impute <- 10

survdat$logtime <- log(survdat$time)

meth <- make.method(survdat)

pred <- make.predictorMatrix(survdat)

pred[,c("time")] <- 0

imp.surv <- mice(survdat, pred = pred, meth = meth, m = n.impute)

# get imputed datasets

imputed <- list()

impc <- complete(imp.surv, action="long")

for(i in 1:n.impute){

imputed[[i]] <- impc[impc$.imp==i, c(3:7, 13:15)]

}

## *Visualize the data*

Here we use the **cmprsk** and **survminer** packages.24,25

library(cmprsk)

ci\_fit <-

cuminc(ftime = survdat.compl$time,fstatus=survdat.compl$status,cencode=0)

library(survminer)

ggcompetingrisks(ci\_fit, xlab = "Days", conf.int = T, multiple\_panels = FALSE)

Chart, line chart

Description automatically generated

## *Fit a prediction model in the imputed datasets*

Using the imputed datasets, we can fit a prediction model. In this example we use a cause-specific Cox proportional hazard regression model and **riskRegression**:26

# Fit cause-specific hazards models ------

library(riskRegression)

fit.model <- list()

for(i in 1:n.impute){

fit.model[[i]] <- CSC(

formula = Hist(time, status) ~ x1 + x2 + x3 + x4 + x5,

data = imputed[[i]]

)

}

We can now use this model to predict the probability of each of the two outcomes for any time point:

prediction.competing <- function(new.patient, single.fit = NULL,

multiple.fit = NULL, time.horizon = NULL, primary.event = NULL){

if(!is.null(multiple.fit)){

ff <- function(i){

predictRisk(

object = multiple.fit[[i]],

cause = primary.event,

newdata = new.patient,

times = time.horizon

)

}

prediction\_matrix <- sapply(1:length(multiple.fit), ff)

if(dim(new.patient)[1] == 1){

prediction <- mean(prediction\_matrix)

} else{

prediction <- apply(prediction\_matrix, 1, mean)

}

} else if(!is.null(single.fit)){

prediction <-

predictRisk(

object = single.fit,

cause = primary.event,

newdata = new.patient,

times = time.horizon

)

}

return(prediction)

}

time.horizon <- 10 ## time point for making predictions

new.patient <- data.frame(x1 = 1, x2 = -1.2, x3 = as.factor(1), x4 = as.factor(0), x5=as.factor(0))

prediction.competing(new.patient, multiple.fit = fit.model, time.horizon = time.horizon, primary.event = 1)

**[1] 0.6059297**

prediction.competing(new.patient, multiple.fit = fit.model, time.horizon = time.horizon, primary.event = 2)

**[1] 0.1649051**

For this patient, the model estimates a 61% probability of experiencing event 1 and 16% probability of experiencing event 2 up until time=10.

We can also plot the predictions across all timepoints:

# plot survival curves

n.points=30

new.patient.prediction=data.frame(time=seq(0,30,length.out=n.points))

for (i in 1:n.points){

new.patient.prediction$new.pred1[i]<-prediction.competing(new.patient, multiple.fit = fit.model, time.horizon = new.patient.prediction$time[i], primary.event = 1)

new.patient.prediction$new.pred2[i]<-prediction.competing(new.patient, multiple.fit = fit.model, time.horizon = new.patient.prediction$time[i], primary.event = 2)

}

predictions.for.plot=data.frame(time=

rep(new.patient.prediction$time,2),

pred=1-c(new.patient.prediction$new.pred1,

new.patient.prediction$new.pred2 ),

event=c(rep("1",n.points), rep("2",n.points)))

ggplot(predictions.for.plot, aes(x = time, y = pred, color = event)) +

geom\_line(aes(group=factor(event)),size=1)

Chart, line chart

Description automatically generated

We will also predict survival for all patients with complete data. We will use this later to assess model’s performance.

#predict for the complete dataset

complete.data <- survdat[complete.cases(survdat[,1:5]),]

predicted.competing.1 <- prediction.competing(complete.data, multiple.fit = fit.model, time.horizon = time.horizon, primary.event = 1)

predicted.competing.2 <- prediction.competing(complete.data, multiple.fit = fit.model, time.horizon = time.horizon, primary.event = 2)

## *Calculate apparent performance of the model*

We can estimate model performance for each of the two competing events separately, starting by calibration, and observed vs. expected (OE) events ratio at a specific time point.

library(survival)

time.horizon<-10

# event 1

primary.event=1

complete.data$event <- factor(complete.data$status, 0:2, labels=c("censor", "event", "competing"))

obj <- summary(survfit(Surv(time, event) ~ 1, data = complete.data), times = time.horizon)

aj <- list("obs" = obj$pstate[, primary.event + 1], "se" = obj$std.err[, primary.event + 1])

# Calculate O/E

OE <- aj$obs / mean(predicted.competing.1)

# For the confidence interval we use method proposed in Debray et al. (2017) doi:10.1136/bmj.i6460

OE\_summary1 <- c(

"OE" = OE,

"lower" = exp(log(OE - qnorm(0.975) \* aj$se / aj$obs)),

"upper" = exp(log(OE + qnorm(0.975) \* aj$se / aj$obs))

)

round(OE\_summary1,2)

**OE lower upper**

1. **0.89 1.10**

# event 2

primary.event=2

complete.data$event <- factor(complete.data$status, 0:2, labels=c("censor", "event", "competing"))

obj <- summary(survfit(Surv(time, event) ~ 1, data = complete.data), times = time.horizon)

aj <- list("obs" = obj$pstate[, primary.event + 1], "se" = obj$std.err[, primary.event + 1])

# Calculate O/E

OE <- aj$obs / mean(predicted.competing.2)

# For the confidence interval we use method proposed in Debray et al. (2017) doi:10.1136/bmj.i6460

OE\_summary2 <- c(

"OE" = OE,

"lower" = exp(log(OE - qnorm(0.975) \* aj$se / aj$obs)),

"upper" = exp(log(OE + qnorm(0.975) \* aj$se / aj$obs))

)

round(OE\_summary2,2)

**OE lower upper**

**0.97 0.78 1.17**

We can also calculate AUC, c-index, and calibration intercept and slope, for each outcome. We use **geepack** and **pec**.27,28 Below we only show for outcome 1:

library(geepack)

library(pec)

calculate\_performance <- function(fit.model = NULL, time = NULL,

status = NULL, data.used = NULL,

time.horizon = NULL, primary.event = NULL){

score\_vdata <- Score(

list("csh\_validation" = fit.model),

formula = Hist(time, status) ~ 1,

cens.model = "km",

data = data.used,

conf.int = TRUE,

times = time.horizon,

metrics = c("auc", "brier"),

summary = c("ipa"),

cause = primary.event,

plots = "calibration" )

pseudos <- data.frame(score\_vdata$Calibration$plotframe)

pseudos <- pseudos[order(pseudos$risk), ]

pseudos$cll\_pred <- log(-log(1 - pseudos$risk))

# Fit model for calibration intercept

fit\_cal\_int <- geese(

pseudovalue ~ offset(cll\_pred),

data = pseudos,

id = ID,

scale.fix = TRUE,

family = gaussian,

mean.link = "cloglog",

corstr = "independence",

jack = TRUE )

# Fit model for calibration slope

fit\_cal\_slope <- geese(

pseudovalue ~ offset(cll\_pred) + cll\_pred,

data = pseudos,

id = ID,

scale.fix = TRUE,

family = gaussian,

mean.link = "cloglog",

corstr = "independence",

jack = TRUE )

AUC <- score\_vdata$AUC$score$AUC

cindex\_csh <- cindex(

object = fit.model,

formula = Hist(time, status) ~ 1,

cause = primary.event,

eval.times = time.horizon,

data = data.used

)$AppCindex$CauseSpecificCox

returnVec <- c("calibration intercept" = summary(fit\_cal\_int)$mean$estimate,

"calibration slope" = 1 + summary(fit\_cal\_slope)$mean["cll\_pred",]$estimate,

"AUC" = AUC,

"c-index" = cindex\_csh)

return(returnVec)

}

apparent.competing.list <- matrix(NA, nrow = n.impute, ncol = 4)

for(i in 1:n.impute){

apparent.competing.list[i,]<-calculate\_performance(fit.model=fit.model[[i]],

time=complete.data$time,

status=complete.data$status,

data.used=complete.data,

time.horizon=time.horizon,

primary.event=primary.event)}

apparent.competing1 <- apply(apparent.competing.list, 2, mean)

names(apparent.competing1)<-c("calibration intercept", "calibration slope", "AUC", "c-index")

round(apparent.competing1,2)

**calibration intercept calibration slope AUC c-index**

**0.02 1.01 0.83 0.78**

(see Section 5.8 on how to obtain uncertainty intervals around these numbers)

Next, we can create a calibration plot for each outcome. Below we only show for outcome 1.

# calibration plot

primary.event<-1

pseudos=list()

smooth\_pseudos=list()

for(i in 1:n.impute){

score\_vdata <- Score(

list("csh\_validation" = fit.model[[i]]),

formula = Hist(time, status) ~ 1,

cens.model = "km",

data = complete.data,

conf.int = TRUE,

times = time.horizon,

metrics = c("auc", "brier"),

summary = c("ipa"),

cause = primary.event,

plots = "calibration"

)

pseudos[[i]] <- data.frame( score\_vdata$Calibration$plotframe)

pseudos[[i]] <- pseudos[[i]][order(pseudos[[i]]$risk), ]

smooth\_pseudos[[i]] <- predict(

stats::loess(pseudovalue ~ risk, data = pseudos[[i]], degree = 1, span = 0.33),se = TRUE)

}

ps.risk=pseudos[[1]]$risk/n.impute; for(i in 2:n.impute){ps.risk=ps.risk+pseudos[[i]]$risk/n.impute}

ps.val=pseudos[[1]]$pseudovalue/n.impute; for(i in 2:n.impute){ps.val=ps.val+pseudos[[i]]$pseudovalue/n.impute}

ps.fit=smooth\_pseudos[[1]]$fit/n.impute; for(i in 2:n.impute){ps.fit=ps.fit+smooth\_pseudos[[i]]$fit/n.impute}

ps.df=smooth\_pseudos[[1]]$df/n.impute; for(i in 2:n.impute){ps.df=ps.df+smooth\_pseudos[[i]]$df/n.impute}

ps.se=smooth\_pseudos[[1]]$se/n.impute;for(i in 2:n.impute){ps.se=ps.se+smooth\_pseudos[[i]]$se/n.impute}

spike\_bounds <- c(-0.075, 0)

bin\_breaks <- seq(0, 0.6, length.out = 100 + 1)

freqs <- table(cut(predicted.competing.1, breaks = bin\_breaks))

bins <- bin\_breaks[-1]

freqs\_valid <- freqs[freqs > 0]

freqs\_rescaled <- spike\_bounds[1] + (spike\_bounds[2] - spike\_bounds[1]) \*

(freqs\_valid - min(freqs\_valid)) / (max(freqs\_valid) - min(freqs\_valid))

# produce plot

plot(

x = ps.risk,

y = ps.val,

xlim = c(0, 0.6),

ylim = c(spike\_bounds[1], 0.6),

yaxt = "n",

frame.plot = FALSE,

xlab = "Estimated risks",

ylab = "Observed outcome proportions",

type = "n"

)

axis(2, seq(0, 0.6, by = 0.1), labels = seq(0, 0.6, by = 0.1))

polygon(

x = c(ps.risk, rev(ps.risk)),

y = c(

pmax(ps.fit - qt(0.975, ps.df) \* ps.se, 0),

rev(ps.fit + qt(0.975, ps.df) \* ps.se)

),

border = FALSE,

col = "lightgray"

)

abline(a = 0, b = 1, col = "gray")

lines(x = ps.risk, y = ps.fit, lwd = 2)

segments(

x0 = bins[freqs > 0],

y0 = spike\_bounds[1],

x1 = bins[freqs > 0],

y1 = freqs\_rescaled

)

Chart, histogram

Description automatically generated

## *Calculate optimism-corrected performance of the model*

We can now use bootstrapping to assess model optimism.

# Internal CV via bootstrapping -------------------

# bootstrap in each multiply imputed dataset

n.bootstrap <- 10

n.impute <- 10

primary.event<-1

time.horizon<-10

optimism.competing.eachbootstrap <- matrix(NA, n.bootstrap, 4)

optimism.competing <- matrix(NA, n.impute, 4)

for (i in 1:n.impute){

for(j in 1:n.bootstrap){

boot.sample <- sample(length(imputed[[i]]$time), replace = T)

# create bootstrap sample

imp.boot <- as.data.frame(lapply(imputed[[i]], function(x){x[boot.sample]}))

# predict in bootstrap

f1 <- as.data.frame(do.call(cbind, lapply(imp.boot, function(x) {as.numeric(as.character(x))})))

# fit cause specific hazard model

fit.competing.boot <- CSC(formula = Hist(time, status) ~ x1 + x2 + x3 + x4,

data = f1)

competing.boot <- calculate\_performance(fit.model = fit.competing.boot,

time = f1$time,

status = f1$status,

data.used = f1,

time.horizon = time.horizon,

primary.event = primary.event)

# predict in test data

f2 <- as.data.frame(do.call(cbind, lapply(imputed[[i]], function(x) {as.numeric(as.character(x))})))

competing.test <- calculate\_performance(fit.model = fit.competing.boot,

time = f2$time,

status = f2$status,

data.used = f2,

time.horizon = time.horizon,

primary.event = primary.event)

optimism.competing.eachbootstrap[j,] <- competing.boot - competing.test

}

optimism.competing[i,] <- apply(optimism.competing.eachbootstrap, 2, mean)

print(paste0("imputation done: ", i))

}

mean.optimism.competing <- apply(optimism.competing, 2, mean)

optimism.corrected.competing <- apparent.competing1 - mean.optimism.competing

round(apparent.competing1,2)

**calibration intercept calibration slope AUC c-index**

**0.016 1.008 0.834 0.778**

round(optimism.corrected.competing,2)

**calibration intercept calibration slope AUC c-index**

**0.020 0.974 0.828 0.772**

Essentially we see no optimism here, which is of course expected due to the large sample size and small size of covariates used in the model.

## *Perform internal-external cross-validation*

We can follow an internal-external cross-validation using the clust variable in the dataset.

# Internal-external CV -------------------

clusters <- unique(survdat$clust)

N.clust <- length(clusters) # 10 clusters in this example

data.in <- data.leftout <- list()

#create the datasets

for(i in 1:N.clust){

data.in[[i]]<- survdat[survdat$clust!=clusters[i],]

data.leftout[[i]]<- survdat[survdat$clust==clusters[i],]

complete.index <- complete.cases(data.leftout[[i]][,c(paste0("x", 1:5))])

data.leftout[[i]] <- data.leftout[[i]][complete.index,]

}

n.impute <- 10

imputed <- fit.competing.CV <- list()

leftout.prediction.competing <- leftout.performance.competing <- list()

for (i in 1:N.clust){

data.in[[i]]$logtime <- log(data.in[[i]]$time)

meth <- make.method(data.in[[i]])

pred <- make.predictorMatrix(data.in[[i]])

pred[,c("time")] <- 0

imp.surv <- mice(data.in[[i]], pred = pred, meth = meth, m = n.impute)

# get imputed datasets

imputed <- list()

impc <- complete(imp.surv, action="long")

for(j in 1:n.impute){

imputed[[j]] <- impc[impc$.imp==j, c(3:7, 13:15)]

}

leftout.performance.competing.each <- matrix(NA, nrow = n.impute, ncol = 4)

for(j in 1:n.impute){

fit.competing.CV <- CSC(

formula = Hist(time, status) ~ x1 + x2 + x3 + x4,

data = imputed[[j]]

)

leftout.performance.competing.each[j,] <- calculate\_performance(

fit.model = fit.competing.CV,

time = data.leftout$time,

status = data.leftout$status,

data.used = imputed[[j]],

time.horizon = time.horizon,

primary.event = primary.event)

}

leftout.performance.competing[[i]] <- apply(leftout.performance.competing.each, 2, mean)

}

# performance per cluster

leftout.performance.competing

int.ext.competing<-data.frame(cluster=1:N.clust,round(matrix(unlist(leftout.performance.competing),nrow=N.clust, byrow = T),2))

colnames(int.ext.competing)=c("cluster","calibration intercept", "calibration slope", "AUC", "c-index")

int.ext.competing

**cluster calibration intercept calibration slope AUC c-index**

**1 1 0.04 0.97 0.82 0.76**

**2 2 0.07 1.01 0.83 0.77**

**3 3 0.02 0.94 0.81 0.76**

**4 4 0.01 1.02 0.84 0.78**

**5 5 0.01 0.93 0.81 0.76**

We see very small variation across clusters.

## *Obtain uncertainty intervals for performance measures*

Finally, we can repeat the calculations of Section 5.5 to also obtain some uncertainty intervals.

### calculate CIs for apparent performance -------

library(geepack)

library(pec)

calculate\_performance <- function(fitmodel = NULL, time = NULL,

status = NULL, data.used = NULL,

time.horizon = NULL, primary.event = NULL, bootstrap=100){

score\_vdata <- Score(

list("csh\_validation" = fitmodel),

formula = Hist(time, status) ~ 1,

cens.model = "km",

data = data.used,

conf.int = TRUE,

times = time.horizon,

metrics = c("auc", "brier"),

summary = c("ipa"),

cause = primary.event,

plots = "calibration" )

pseudos <- data.frame(score\_vdata$Calibration$plotframe)

pseudos <- pseudos[order(pseudos$risk), ]

pseudos$cll\_pred <- log(-log(1 - pseudos$risk))

# Fit model for calibration intercept

fit\_cal\_int <- geese(

pseudovalue ~ offset(cll\_pred),

data = pseudos,

id = ID,

scale.fix = TRUE,

family = gaussian,

mean.link = "cloglog",

corstr = "independence",

jack = TRUE )

# Fit model for calibration slope

fit\_cal\_slope <- geese(

pseudovalue ~ offset(cll\_pred) + cll\_pred,

data = pseudos,

id = ID,

scale.fix = TRUE,

family = gaussian,

mean.link = "cloglog",

corstr = "independence",

jack = TRUE )

AUC <- score\_vdata$AUC$score$AUC

se.AUC <- score\_vdata$AUC$score$se

### CI bootstraps

boots\_ls <- lapply(seq\_len(bootstrap), function(b) {

vdata\_boot <- data.used[sample(nrow(data.used), replace = TRUE), ]

cindex\_boot <- pec::cindex(

object = fitmodel,

formula = Hist(time, status) ~ 1,

cause = primary.event,

eval.times = time.horizon,

data = vdata\_boot,

verbose = FALSE

)$AppCindex$CauseSpecificCox

cbind.data.frame("cindex" = cindex\_boot)

})

cindex <- do.call(rbind.data.frame, boots\_ls)

#####

returnVec <- c("cal.int" = summary(fit\_cal\_int)$mean$estimate,

"cal.int.se"=summary(fit\_cal\_int)$mean$san.se,

"cal.slope" = 1 + summary(fit\_cal\_slope)$mean["cll\_pred",]$estimate,

"cal.slope.se"=summary(fit\_cal\_slope)$mean["cll\_pred",]$san.se,

"AUC" = AUC,"se.AUC"=se.AUC,

"c.index" = cindex)

return(returnVec)

}

apparent.competing.list <- list()

cindex=c(); auc=c(); se.auc=c(); cal.int=c();cal.int.se=c();cal.slope=c();cal.slope.se=c()

for(i in 1:n.impute){

apparent.competing.list[[i]]<-calculate\_performance(fitmodel=fit.model[[i]],

time=complete.data$time,

status=complete.data$status,

data.used=complete.data,

time.horizon=time.horizon,

primary.event=1,

bootstrap=10)

cindex=c(cindex, apparent.competing.list[[i]]$c.index)

auc=c(auc,apparent.competing.list[[i]]$AUC )

se.auc=c(se.auc, apparent.competing.list[[i]]$se.AUC)

cal.int=c(cal.int,apparent.competing.list[[i]]$cal.int)

cal.int.se=c(cal.int.se,apparent.competing.list[[i]]$cal.int.se)

cal.slope=c(cal.slope,apparent.competing.list[[i]]$cal.slope)

cal.slope.se=c(cal.slope.se,apparent.competing.list[[i]]$cal.slope.se)

}

apparent.cindex=round(c(mean(cindex), quantile(cindex, probs = c(0.025, 0.975)) ),2)

apparent.se.auc=sqrt(mean(se.auc^2)+(1+1/n.impute)/n.impute\*(sum((mean(auc)-auc)^2)))

apparent.AUC=round(c(mean(auc), mean(auc)-1.96\*apparent.se.auc, mean(auc)+1.96\*apparent.se.auc),2)

names(apparent.AUC)=c("mean", "2.5%", "97.5%")

apparent.se.int=sqrt(mean(cal.int.se^2)+(1+1/n.impute)/n.impute\*(sum((mean(cal.int)-cal.int)^2)))

apparent.se.slope=sqrt(mean(cal.slope.se^2)+(1+1/n.impute)/n.impute\*(sum((mean(cal.slope)-cal.slope)^2)))

apparent.int=round(c(mean(cal.int), mean(cal.int)-1.96\*apparent.se.int, mean(cal.int)+1.96\*apparent.se.int),2)

names(apparent.int)=c("mean", "2.5%", "97.5%")

apparent.slope=round(c(mean(cal.slope), mean(cal.slope)-1.96\*apparent.se.slope, mean(cal.slope)+1.96\*apparent.se.slope),2)

names(apparent.slope)=c("mean", "2.5%", "97.5%")

# results

apparent.cindex

**2.5% 97.5%**

**0.78 0.74 0.81**

apparent.AUC

**mean 2.5% 97.5%**

**0.83 0.80 0.87**

apparent.int

**mean 2.5% 97.5%**

**0.02 -0.15 0.18**

apparent.slope

**mean 2.5% 97.5%**

**1.01 0.80 1.21**

## *Decision curve analysis*

Here we first need to provide the primary event of interest and a time point.

### Decision curve analysis

primary.event<-1

time.of.interest<-15

predicted.for.dca1 <- prediction.competing(complete.data, multiple.fit = fit.model,time.horizon = time.of.interest, primary.event = 1)

for.dca=data.frame(time=complete.data$time, status=complete.data$status, pred=predicted.for.dca1)

for.dca$status[for.dca$status!=primary.event]=0

dca1<-dca(Surv(time, status) ~ pred,

data = for.dca,thresholds = 1:100 / 100,

time = time.horizon)

plot(dca1,smooth = TRUE)

Chart, line chart

Description automatically generated

We see that the model performs better than both treat all and treat none strategies for thresholds above 5%.

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