Model Evaluation

Considerations for Time-to-Event Studies

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Overview

1. Time to Event Studies
   - What differentiates a TTE Study from other studies?
2. Classical Model Evaluation: Brier Score and AUC
   - What are classical model evaluation tools & why can't we use them?
3. TTS Model Evaluation: IBS and c-index
   - How do these methods address the limitations of classical methods?
4. Discussion
   - What measure is most useful for machine learning in TTS?
5. Further Considerations
   - What other methods are coming?

Time-to Event Studies

- Analysis working with (right) censored data
- Right censored data (event after follow up) vs. left censored data (event was not recorded when it occurred initially)
- Highly relevant for clinicians in the field of medical statistics e.g. looking at when a patient dies or when he gets a disease (clinical/epidemiological studies)
- In Economics/Finance e.g. to examine when a subject/borrower will default or when a subject will find/lose a job
- Operations research to predict the time a machine will break

Basic Notations & Concepts

- Time T and Survival S
- From hazard to cumulative hazard to survival
- Hazard h(t,x) is the eminent probability of death a specific point in time
- Capital H is the cumulative hazard
- non-parametric hazard models (KM) vs.semi-parametric proportional hazard model

Classical Model Evaluation Tools for Classification Tasks

1. **Diagnostic vs. Prognostic Study**
2. **What elements do we consider?**
   - Discrimination: Are we able to correctly discriminate between e.g. sick and healthy patients ?
   - Calibration: How concise is our prediction accuracy ?
   - Clinical Usefulness: Will our model create more benefits than harm?
3. Working with *Label* vs. working with *Probability*
   - Brier Score (probability from true class label)
   - AUC (label based error measure via specificity and sensitivity)

Brier Score

Based on loss function. Other loss measures are the log loss or the integrated log loss.

MSE for Regression (L2 Loss):

$MSE = \frac{1}{n}\sum_{i=1}^{n}(y^{(i)}) - \hat{y}^{(i)})^2$

Where: the $MSE \in [0; \infty)$

The Brier Score is the MSE for Classification:

$BS = \frac{1}{n}\sum_{i=1}^{n}(\hat{\pi}(x^{(i)}) - y^{(i)})^2$

The general version of the brier score looks at a specific point in time We can plot this brier score via prediction error curves (pec)

Confusion Matrix

Sensitivity or: true positive rate

- deals with values above the threshold among the subject group which do endure an event

$TPF = \frac{TP}{TP+FN}$

Specificity or: true negative rate

- deals with false negatives, hence patients with a disease we classify as not having any diseases

$TNR = \frac{TN}{TN+FP}$

Why cant we use traditional model evaluation tools for time to event studies?

- Working with censored data
- Account for time dependent covariates

Early approaches: - excluding subjects with right censored data and only evaluate on the complete data

From AUC to Harell's C-index to time dependent C-index

- Advancement from AUC
- Rank correlation measure but still have to deal with censoring
- studying concordance (∼consistency) and discordance (∼inconsistency) pairs

Intuitively speaking the difference between AUC and c-index is as follows:

$AUC = $ $C = $ While C is defined as:

$\frac{\# ConcordantPairs}{\# ConcordantPairs + \# DiscordantPairs}$

In this approach, only comparable pairs are evaluated

$C^{td} = \frac{\pi_{concordance}}{\pi_{comparable}}$

Henceforth:

$C^{td} = \frac{Pr(z(X_i) > z(X_j) \& T_i < T_j \& E_i = 1}{Pr(Ti < Tj | E_i = 1)}$

c-index

How to deal with censoring: * addressing right censored data via inverse of the probability of censoring weighted estimate (of concordance probability) * Kendall rank correlation coefficient test as inspiration * Summary measure (over all time) based on the AUC

$$C - index = \frac{\Delta_j \times \sum_{i,j} 1_{Ti > Tj} \times 1_{\eta_i > \eta_j}}{\Delta_j \times \sum_{i,j} 1_{Ti > Tj}}$$

IBS

- called cumulative predictive error curves == continuous ranked probability score (crps)
- area under the prediction error curve
- Integral over all points in time to get one summary value henceforth called "integrated" BS
- able to build a Rˆ2 like measure where we divide MSE of a model with a different MSE of reference model
- Where L is a loss function of the S(the probability that the event of interest has not taken place yet) and time
- t is the time of the event (death) and t* the time before death
- G(t) is the P(C>t), so where the censored time is longer than the time (in mlr3proba via survfit == KM Estimate)
- When selecting integrated == FALSE then we looking at specific time

Mean population

Mean Population:without Integration

$$L(S,t|t^*) = \frac{1}{N}\sum_{i=1}^{N} L(S_i, t_i|t^*) \tag{9}$$

Mean Population: with Integration

$$L(S,t|t^*) = \frac{1}{NT}\sum_{i=1}^{N}\sum_{j=1}^{T} L(S_i, t_i|t^*)$$

- N = Number of observations
- S_i is the predicted survival function

Coding Settup

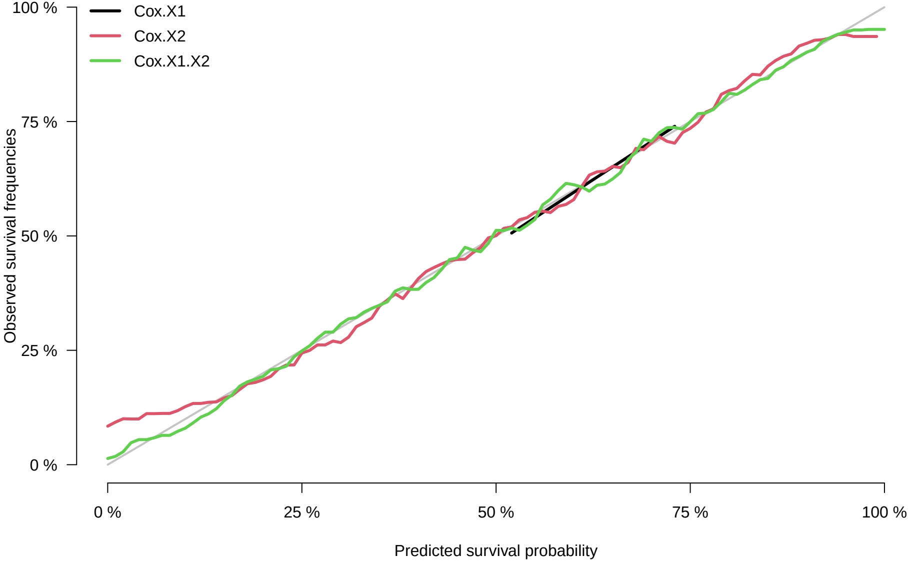
```r
set.seed(123)
dat=SimSurv(10000)
models <-  list("Cox.X1"=coxph(Surv(time,status)~X1,
                      data=dat, x=TRUE,y=TRUE),
               "Cox.X2"=coxph(Surv(time,status)~X2,
                      data=dat,x=TRUE,y=TRUE),
               "Cox.X1.X2"=coxph(Surv(time,status)~X1+X2,
                      data=dat,x=TRUE,y=TRUE))
```

Defining the prediction error based on the brier score

```
perror <- pec(object=models,
                 formula=Surv(time,status)~1,
              data=dat,
                 exact=TRUE, cens.model="marginal",
              splitMethod="none",
                 B=0,# number boostrap samples
                 verbose=TRUE)
```

Calibration Plot

```
calPlot(models)
```



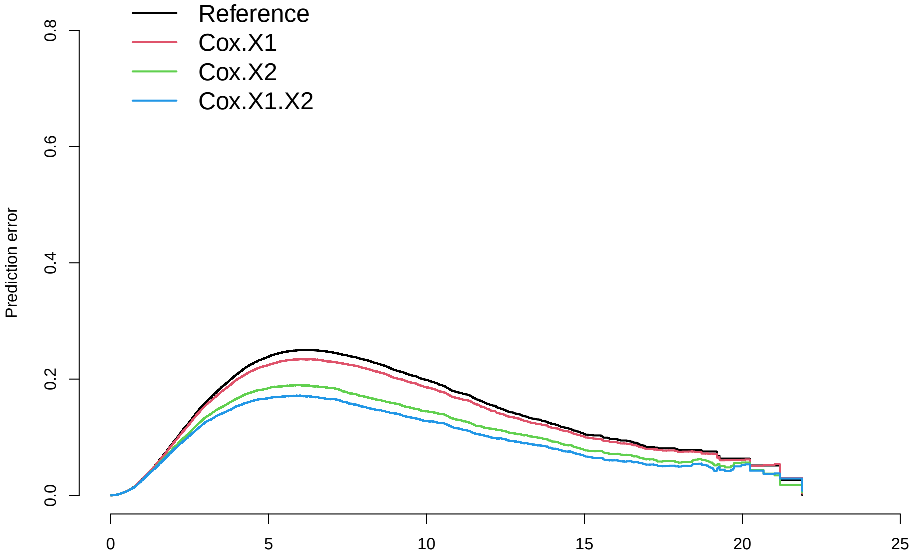
Summary Prediction Error Curve

```r
summary(perror,times= quantile(dat$time[dat$status==1], c(.25, .5, .75,1)))
```

```
##
## Prediction error curves
##
##
## No data splitting: either apparent or independent test sample performance
##
##  AppErr
##     time n.risk Reference Cox.X1 Cox.X2 Cox.X1.X2
## 1  2.568   7892     0.132  0.128  0.112     0.106
## 2  4.270   5644     0.220  0.208  0.174     0.159
## 3  6.513   3179     0.249  0.233  0.188     0.169
## 4 21.189      1     0.026  0.030  0.018     0.029
```

Plotting prediction error

```
plot(perror,xlim=c(0,25), ylim = c(0,0.8))
```



Cumulative Prediction Error

```
#crps(object, models, what, times, start)
crps(perror,times= quantile(dat$time[dat$status==1], c(.25, .5, .75, 1)))
```

```
##
## Integrated Brier score (crps):
##
##             IBS[0;time=2.6) IBS[0;time=4.3) IBS[0;time=6.5) IBS[0;time=21.
## Reference             0.051           0.102           0.150            0.1
## Cox.X1                0.050           0.099           0.143            0.1
## Cox.X2                0.046           0.086           0.120            0.1
## Cox.X1.X2             0.044           0.081           0.111            0.0
```

```
# ibs(perror,times= quantile(dat$time[dat$status==1], c(.25, .5, .75, 1)))
```

cindex Implementation

Components of the c-index function

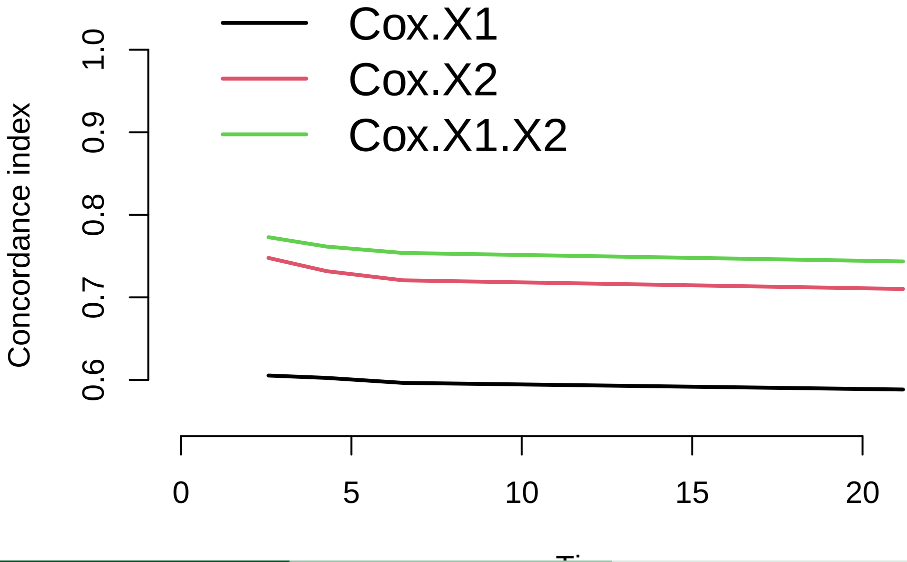
cindex(*object, formula, cens.model,data, eval.times, cause, data, splitMethod, B,M. . .*)

- **formula** is our survival formula (Surv(time,status)∼x1+x2 for cens.model="cox" or Surv(time,status)∼1 for cens.model ="marginal")
- **cens.model** is our method for estimating the inverse probability of censoring weights (e.g. cox, marginal, nonpar)
- **splitMethod** is the internal validation design, B the number of boostrap samples & M the size of the boostrap sample
- **cause** used for competing risks (default is the first state of the response)

```
cindex = cindex(models, formula = Surv(time,status) ~ 1,
     cens.model="marginal", data = dat,
      eval.times= quantile(dat$time[dat$status==1], c(.25, .5, .75,1)))
```

c-index plot

```r
plot(cindex,xlim=c(0,24), ylim =c(0.55,1))
```



mlr3Proba

Methods based on the loss function:

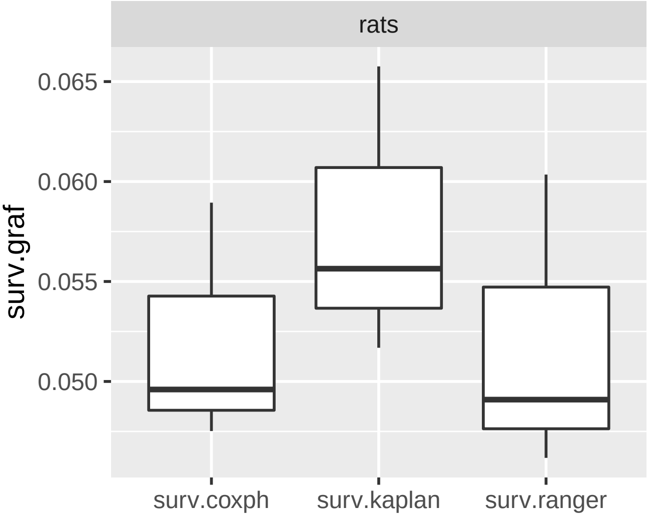
- Integrated Graf Score (other Name for IBS based on Author Graf)
- Integrated Log Loss (surpress scale of variation)
- Log Loss (censored data ignored)

Further measures via survAUC package:

- Uno's AUC
- Song and Zhou's AUC

mlr3Proba Example

```
autoplot(bmr, measure = measure)
```



Discussion

- c-index has gained popularity because of it's interpretability
- Integrated Brier Score accounts for both calibration and discrimination
- Irrespective, neither model accounts and leaves room for improvement
- IBS allows for differentiation of 'useless' and 'harmful'
- Estimators can be influenced by data
- Clinical consequences problematic

Novel Research

- Decision Curve Analysis (clinical consequences): plotting different exchange rates with the net benefit equation
- Net Reclassification Improvement (clinical consequences)
- Other estimators like SVM estimators for the evaluations tools for the censored data
- IPA
- Competing Risks

Conclusion

- There are various different modifications for model evaluation, neither being unconditionally superior
- The Brier Score and the AUC are pivotal for many of these methods
- While there has been a lot of research on this topic, the debate is on going

Literature and Recommendations

Introduction:

- Steyerberg, E. W., Vickers, A. J., Cook, N. R., Gerds, T., Gonen, M., Obuchowski, N., . . . & Kattan, M. W. (2010). Assessing the performance of prediction models: a framework for some traditional and novel measures. Epidemiology (Cambridge, Mass.), 21(1), 128.

Comparative Study:

- Kattan, M. W., & Gerds, T. A. (2018). The index of prediction accuracy: an intuitive measure useful for evaluating risk prediction models. Diagnostic and prognostic research, 2(1), 7.

Use Cases:

https://rpubs.com/kaz_yos/survival-auc https://datascienceplus.com/time-dependent-roc-for-survival-prediction-models-in-r/
https://rdrr.io/cran/pec/ https://adibender.github.io/pammtools/