Model Evaluation for Time to Event Studies

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Introduction

Time to event studies frequently introduce the challenge of working right censored data, a common characteristic survival data used e.g. in clinical and epidemiological studies . Right censored data is data that does not entail the occurrence of events for every subject. Reasons for that can be manifold but one example would be that the study ends prior to the event occurring. This paper will provide a overview a number of model evaluation metrics and respective modifications for time to event studies, focusing predominately on popular extensions of the loss function and the receiver operating characteristic curve, namely the IBS and the c-index.

The c-index does enjoy considerably prominence among clinicians due to interpretability and the ability to make comprehensive conclusions for the individual subject. Irrespective, the c-index only considers discrimination and does not account for calibration as an evaluation criterion is a pivotal shortcoming when assessing prognostic studies. Henceforth, this paper suggests that the integrated brier score is the preferable tool for model evaluation. For completeness, there will be a brief outline of potential new measures.

The paper is structured as follows:

I will introduce the integrated brier score, providing further information on the origin, theoretical underpinning and the respective characteristics. I will introduce the c-index, following the same procedure as with the integrated brier score. Following the analysis of these two cornerstones of model evaluation for time to event studies, i will illustrate further methods and current research within the field. Subsequently, the fourth section will provide an example of how to implement given methods in R. Lastly, the conclusion will summarize core findings of this brief comparative study.

Model Evaluation metrics

When attempting to evaluate a model performance, there are various components to consider. Firstly, one needs to differentiate between the type of study at hand, namely whether we are dealing with 'prognostic studies' or 'diagnostic studies'.

Diagnostic and Prognostic studies

In a clinical setting, studies can be separated into diagnostic and prognostic studies. Diagnostic studies are concerned with the problem of how to classify a patient at this point in time. For binary classification tasks during diagnostic studies, where we need separate between e.g. patients with

and without disease, discrimination is a crucial concern. Prognostics on the other hand deals with predictive modeling. For prognostic studies, we need to ensure that

Now, we can disentangle the different components of model evaluation. Model evaluation differentiates between discrimination and calibration. A third prominent evaluation criteria is clinical usefulness which will be discussed later.

Discrimination

Discrimination is the ability of a model to handle patients that do not have outcomes accordingly. Inevitably, when controlling for discrimination, we are controlling for how well our model is handling subjects with outcomes as compared to subjects without outcomes. Therefore, as the name suggest, we are testing how strong our model discriminates between subjects that incur an event versus subjects that don't. Discrimination is an important pillar for model evaluation in survival analysis. Various measures have emerged, that deal with discrimination such as the c-index or the net reclassification index. Perfect discrimination would imply that all our subjects with the event have higher scores than subjects that do not have an event within their time period. One should note that when using a model that only controls for discrimination, our predictive accuracy could be horrible but as long as this condition holds, inaccurate models could be evaluated falsely as superior.

Origin ROC / Concordance-statistics

The Receiver Operating Characteristic Curve (ROC) is an important model evaluation tool, gaining substantial prominence in various fields. In a nutshell, the ROC takes into account two factors namely sensitivity and specificity. One should note that there are many names for these factors, but essentially all describing the same thing. Firstly, Sensitivity deals with the likelihood of positive test results. Specifically sensitivity deals with values above the threshold among the subject group which do endure an event e.g. the subjects with diseases (Cook, N. 2007).

Sensitivity becomes more volatile when for instance dealing with milder, nuanced cases of a disease. Another name frequently used for Sensitivity is the true positive rate.

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

On the other hand, specificity deals with false negatives, patients with a disease we classify as not having any diseases. However, specificity is especially subject to the influence of the characteristics of a subject without disease. Another name for specificity is the true negative rate.

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

Examples of such characteristics are age or gender. The ROC takes these two factors and plots sensitivity against 1- specificity. The area under the curve or the c statistic ranges from 0.5 (no discrimination) to max of 1 (perfect discrimination) Essentially, the c statistic is equivalent to the probability that the measure or predicted risk is higher for a case than for a non-case. Further, c-statistic describes how well models rank case and non-case, but not a function of predicted probabilities. The c statistic is a rank correlation measure, focusing on Kendall's tau (Uno et al., 2011). Because c statistics is based on ranks it is less sensitive than e.g. measures based on likelihood (e.g. loss functions).

C-index

Due to the fact that we deal need to be able to deal with censored data, we need to modify the ROC. The c- index is the generalization of the ROC for survival data (Cook, N., 2007). Alternatively, there are a number of time dependent measures and modification of this method and the ROC curve, interesting for time to event studies.

Modifications

Antolini et al. (2005) propose a time dependent c-index, where discrimination is summarized over time. Their model considered the presence of a population feature rather than a shortcoming of the sample. Irrespective, they also agree with the common consent and propose the use the c-index in symbiosis with a tool to measure calibration for model evaluation. One shortcoming of the c-statistics is that it does not account for time dependence.

Heagerty and Zheng (2005) introduce 3 modifications of the AUC, namely the (1) cumulative sensitivity and dynamic specificity (C/D), (2) incident sensitivity and dynamic specificity (I/D) and (3) incident sensitivity and static specificity (I/S).

cumulative sensitivity and dynamic specificity: Cumulative sensitivity describes the likelihood of a subject to experience a higher score among those who already experienced the event prior to time t. Dynamic specificity is the counterpart, looking at the likelihood of subjects to have lower scores among the event free subjects surpassing point t (Kamarudin et al., 2017). This method is considered useful when dealing having specific points of time in mind. As this is often the case, this method has frequently found application in clinical studies (Kamarudin et al., 2017).

incident sensitivity and dynamic specificity: Here sensitivity is the likelihood of a subject to have a greater score among the individuals who have the event taking place at a the time point t. Respectively, the specificity is the likelihood of a subject to have a lower score among the individuals who dont have the event taking place in time t. This measure is less frequently used and mostly not the focus of clinical studies.(Kamarudin et al., 2017).

incident sensitivity and static specificity: The sensitivity is again the likelihood of a subject to have a greater score among the individuals who have the event taking place at a the time point t while the control is an event free individual for a fixed follow up period. As the second and third modification are rarely used, scholarship usually only focuses on the C/D variation.(Kamarudin et al., 2017).

$$AUC^{I,D}(t) = P(X_i > c|T_i > t) \tag{5}$$

$$C^T = \int_0^T AUC^{I,D}(t) w^T(t) dt \tag{6}$$

Advantages

The c-index has gained popularity because so interpretable (Kattan and Gerds, 2018). Especially for the individual patient in diagnostic studies, this method has gained popularity. Further, there are lots of modifications of this method.

Performance is not assessed relative to a different model. Therefore evaluation does not require pairs of patients, which is more realistic.

Disadvantages

While for diagnostic studies, discrimination is the most important feature for a model evaluation metric, the same is not true for prognostic studies. Henceforth, using a concordance statistic for prognostic studies is not advised.

Estimators can be influenced by data

As mentioned above, for a more nuanced prevalence of a disease, the sensitivity is affected and henceforth problematic (Cook,N., 2007). Specificity is dependent on the data structure, but as suggested by Cook (2007), specificity is for instance affected by age, gender and the prevalence of concomitant risk factors.

Clinical consequences

For instance, other important questions could be whether introducing either model in the first place, or rephrased whether any of these models cause a net benefit. This argument is related to the analogy of Kattan and Gerds (2018), arguing that model evaluation metrics needs to be able to differentiate between useless and harmful models. Harmful models are models that make incorrect predictions while useless models always predict prevalence. The c-index does not account for clinical consequences and the subjective importance of false positives relative to false negatives. This problem holds for both the c-index and the brier score but generally speaking, clinical cost are different than specified in these method.

Accounting for time

Further Kattan and Gerds (2018) argue that model evaluation needs to account for the time horizon.

Calibration

When dealing with an prognostic analysis, calibration can become an important concern. Calibration captures the accuracy of our predictions of our model. One ways to measure calibration is for instance the Hosmer-Lemeshow test, the "goodness of fit" test. (Gerds and Schumacher, 2006). Another popular method is the the integrated brier score, a score that controls for both discrimination and calibration.

Uno et al.(2011) propose a modified c-statistic which is consistent for population concordance measures.

Brier Score

Introduction and origin story

The score brier was initially used for weather forecasting (Graf et al., 1999). With uni-dimensional predictions the brier score is the same as the mean squared error. Other terminology that you might encounter is the predicted error or mean squared loss function (Schoop et al.,2011; Gerds

& Schumacher, 2006). Henceforth, some of the applications e.g. in the 'pec' package use other terminology for the brier score.

Explanation of Method

The mean squared error in a nutshell is the incurred quadratic loss, studying the predicted and the true event status (Schoop et al.,2011). Graf et al. (1999) state that the "...expected brier score may be interpreted as a mean squared error of prediction when the estimated prob, which take values in interval [0,1] are viewed as prediction of event status at t,$I(T>t)$ in {0,1}." The brier score is dependent on the evaluation time. By introducing a reweighing scheme, one derives quantities that are independent on the censoring distribution and hence suitable for censored data (Graf et al.,1999). To get a comprehensive time dependent model performance, multiple time points have to be studied.

For the individual at time t:

$$L(S,t|t^*) = [(S(t^*)^2)I(t) \leq t^*, \delta = 1)(\frac{1}{G(t)})] + [((1 - S(t^*))^2)I(t > t^*)(\frac{1}{G(t^*)})] \tag{8}$$

For the population mean:

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

Modifications

Integrated population mean version:

$$L(S,t|t^*) = \frac{1}{NT}\sum_{i=1}^{N}\sum_{j=1}^{T} L(S_i, t_i|t^*) \tag{10}$$

Wu and Lee (2014) advocate for the usage of the sBrier score. In a nutshell, the sBier score is the mean squared error for the current model divided by the mean squared error for the null model.

Advantages

The integrated brier score is a measure accounting for both discrimination and calibration separately , henceforth it more holistic. Graf et al. (1999) argue that the method is more sophisticated than the c-index because it deals with probabilities allowing us insights into the accuracy of our predictions rather than (mis-)classifications. As mentioned, the integrated brier score has the ability to differentiate between useless and harmful models. With e.g. Harell's c index, one is unable to differentiate between the two (Kattan and Gerds, 2018).

Disadvantages

Kattan and Gerds (2018) suggest that the evaluation is somewhat problematic with respect to numerous aspects. The benchmark of the different models are dependent on the overall prevalence of the event in our data set. Henceforth, when working with data where the event rarely takes place, the benchmark becomes convoluted (Kattan and Gerds, 2018).

Interpretation in Pairs

One pivotal shortcoming of the method is the inability to compare results independent from other models. Hence, one is at best only able to see that the one method is superior to the other models at hand. Especially in a practical setting, when undertaking a diagnosis for a patient this is rather impractical as patients don't come in pairs.

Clinicial consequences

We are unable to see whether the implementation of the model is advisable in the first place. Steyerberg et al. (2010) argue that one is unable to detect whether the implementation will cause more harm than benefit. Therefore, some scholars have advocated for complementary tests, to assess the overall profitability of implementing such measures. These complementary tests account for clinical consequences, or in other words more realistic weights given the preferences of clinicians. Clinicians usually don't value the different components of model accuracy equally as their clinical consequences are not equivalent. For example, sending a sick patient home, in the believe of being healthy can do more damage than testing further on a healthy patient, that has been tested sick.

Reclassification

Steyerberg, E. W., Vickers, A. J., Cook, N. R., Gerds, T., Gonen, M., Obuchowski, N., ... & Kattan, M. W. (2010)

- Change is risk stratification.
- Use observed incidence of events of the reclassification table to predicted probabilities of the orgn. model.
- Cook proposing variant og hosmer lemeshow statistic within the reclassified categories, leading to chi-squared statistic.

Net Reclassification improvement Cook (2008) argues that Net reclassification improvement (NRI) and calibration tests for cross classified categories can be used to study the clinical usefulness. While NRI is only a measure to study discrimination, it allows to account for the formation of categories based on clinical risk estimates. Therefore, this measure is also focusing on the clinical application, rather than holistic model evaluation. Henceforth, reclassification might just complement existing clinicians in practical applications as opposed to providing a dominant model evaluation tools.

Cook, N. R., & Ridker, P. M. (2009). Advances in measuring the effect of individual predictors of cardiovascular risk:

- Integrated discrimination improvement
- IDI is equivalent to testing whether the regression coefficient in a model is equl to zero (similar to R^2 or the proportion of variance explained)
- The NRI and the IDI both condition on the case-control or later disease status
- A limitation of NRI and other reclassification measures is that they depend on the particular categories used
- Suggest that reclassification calibration statistic and NRI may be useful in demonstrating the ability of new models and markers to change risk strata and alter treatment decision

Pencina, M. J., D'Agostino Sr, R. B., D'Agostino Jr, R. B., & Vasan, R. S. (2008). Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond

Decision Analysis Curve

One fundamental problem of the methods that we have introduced is that it does not really accommodate the interests of clinicians. From the perspective of a clinician, giving false positive and false negatives the same weight does not make any sense. For instance lets say we result in a false negative for a cancer patient, the patient is harmed to a detrimental extend and deprived of the opportunity to undertake earlier action. Moreover, these methods do not really tell us whether introducing the new model creates added value. Further, preferences may differ from a clinical standpoint. E.g. sensitivity and specificity are frequently unequal in importance to a clinician. Henceforth, scholars have proposed a new complementary framework to assess the net benefit of a model, providing a tool to assess whether implementing a new model is worth it in the first place (Vickers, A., Elkin, E., 2006). Decision analysis curve enables the use of weights, allowing optimal decision making based on subjective preferences, embodied in a net benefit equation. Further Vickers et al. (2016) illustrate that harm is transformed, using an exchange rate to put harm and benefit on one scale. This exchange rate can be obtained by asking clinicians questions based on their subjective preferences such as how many patients they would have undergo a biopsy prior to finding a cancer or weighing the benefits of getting early findings as opposed to the cost of harmful further testing. Together these elements build the net-benefit equation. Plotting different exchange rates with the net benefit equation, gives us the decision analysis curve. The curves enable the practitioner the identification of the rage of threshold probabilities for when a model would be of value, providing information on the necessary benefits needed for a model to be useful and which of many models is optimal (Vickers, A., Elkin, E., 2006). One important consideration is that decision analysis curve is a complement, not a substitute to existing models (Vickers, A., Elkin, E., 2006).

Other proposals

TOC

Implementation

Notable packages:

'pec':

- cindex()
-

'survival': concordance() function

'survIDINRI':

Discrimination Plot

A c-index above the threshold of 0,8 can be considered good (Zhang et al.,2018).

Researchers have combined the usage of reclassification tools with discrimination measures.

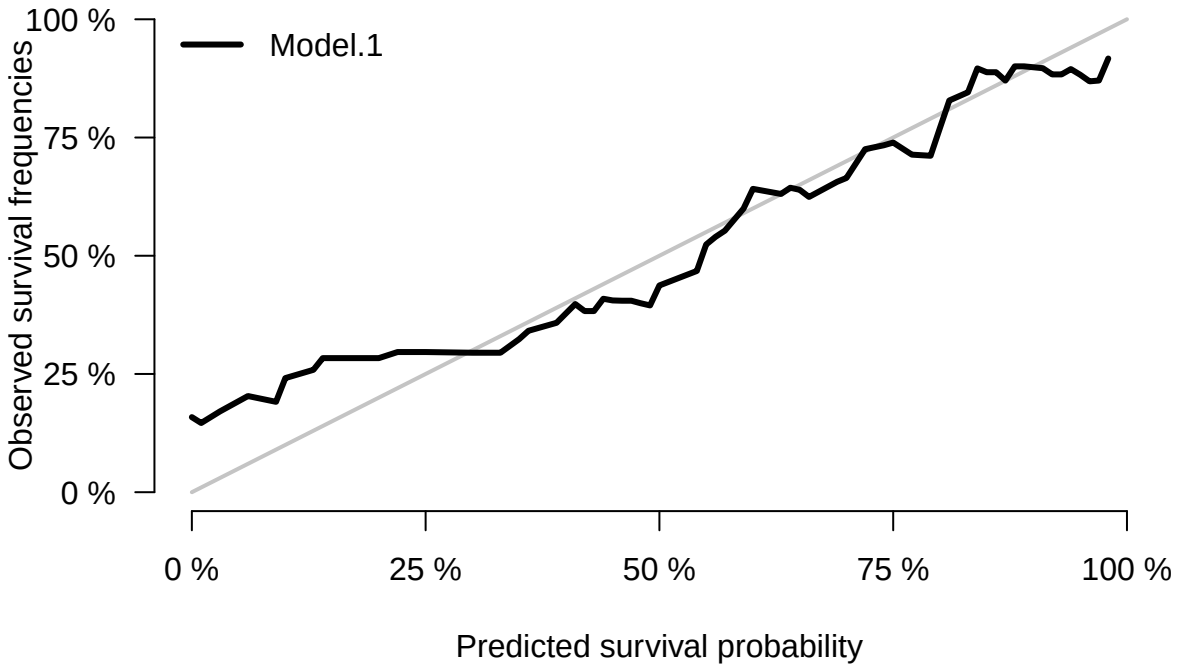
Net reclassification and integrated discrimination improvement implementation

One example package dealing

Calibration Plot

We can use calibration plots to visualize the calibration of our model. The 'pec' packages provides the 'calPlot' function.

```
calPlot(pmodel)
```



mlr3 implementation

Sonabend et al. (2020) provide a package for the mlr3 framework, namely mlr3proba. An useful component is the benchmarking feature of different model evaluation measures. The mlr3proba entails 5 different measures directly namely:

- van Houwelingen's Alpha Calibration
- van Houwelingen's Beta Calibration
- Integrated Graf Score
- Integrated Log Loss
- Log Loss

Further measures via survAUC package:

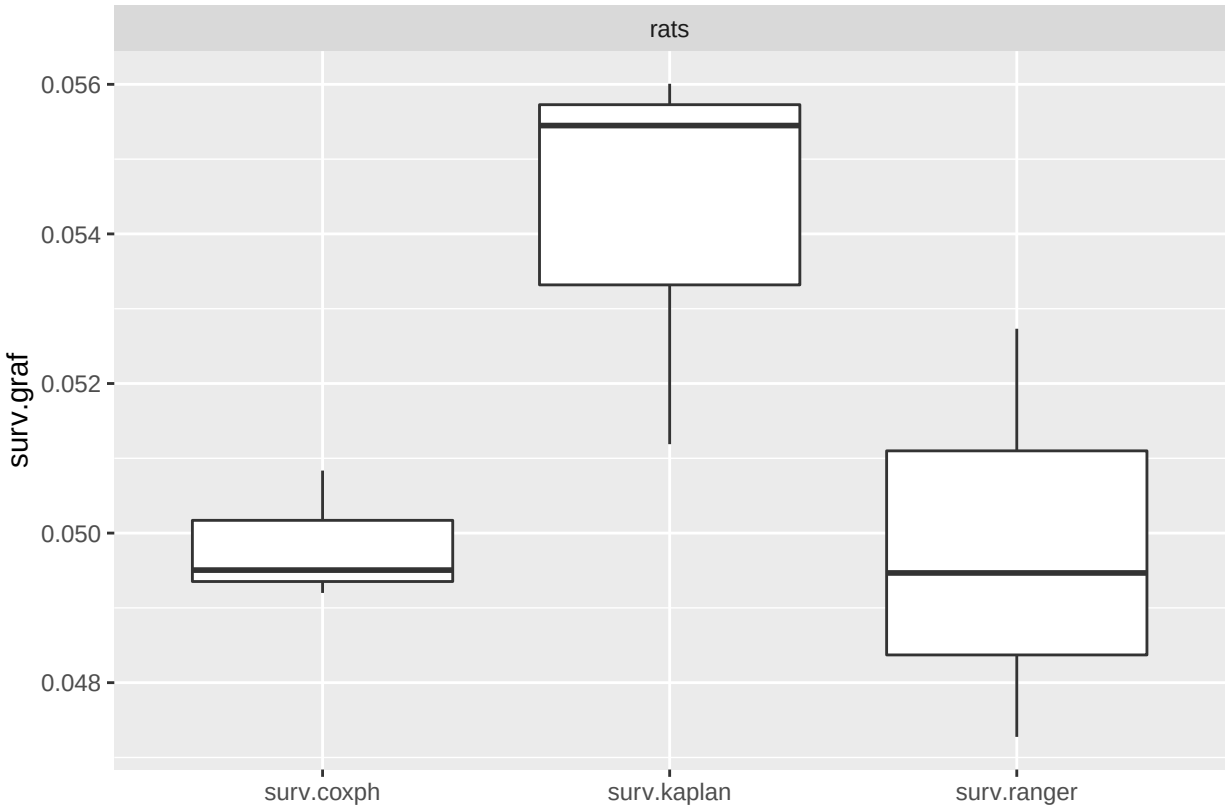
- Uno's AUC/TPR/TNR
- Song and Zhou's AUC/TNR/TPR

Song, X., & Zhou, X. H. (2008). A semiparametric approach for the covariate specific ROC curve with survival outcome. Statistica Sinica, 947-965.

- Chambless and Diao's AUC

- Hung and Chiang's AUC
- Nagelkerke's R2
- O'Quigley, Xu, and Stare's R2
- Xu and O'Quigley's R2

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



Conclusion

Time to event studies require adjusted model evaluation tools for censored survival data. At the core, studies separate between models that evaluate overall performance, discrimination and calibration. Both the c-index for discrimination, and the IBS for discrimination and calibration, are well established tools to undertake model evaluation. New methods such as reclassification and clinical usefulness have gained prominence among scholarship.

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