

# Time to Event Machine Learning - Evaluation

Daniel Saggau

11/9/2020

## Graf et al 1999

### Introduction

- Point prediction of event free times inevitably gives poor results
- Second approach is predicting the survival of event status at fixed point in time, diminishing the expected misspecification/error.
- 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  $\{0,1\}$ .
- **Advantage:** More sophisticated to use estimated probabilities for prediction: Diagnostic test based on predictive values ; probabilities of positive or negative disease status rather than classification of diseased or not diseased.
- Therefore: brier score, measures average discrepancies between true disease status and predicted value, better than misclassification rate

### Conclusion

- Make statement that time to event itself cannot adequately be predicted.
- Best at  $t=0$  is try to estimate the probability that the event of interest will not occur until  $t^*$ .
- Therefore, measure **needs to compare estimates of event free probabilities**
- **Criticism:** ROC methodology cannot capture feature of prognostic classification: Applies to c-index and index of concordance
- c-index has interpretation of the area under the ROC curve for an artificially constructed diagnostic test in the survival context
- Brier and log score are well investigated and according to paper need to be implemented in SA.
- Summary measures of inaccuracy may be obtained by using loss functions integrated with respect to suitable weight function
- Introduce re-weighting scheme, leading to quantities that don't depend on censoring distribution asymptotically

## P.Wang 2017 Machine Learning for Survival Analysis

- Named after Glenn W. Brier and initially used for inaccuracy of probabilistic forecasts
- Can only be used with probabilistic outcomes  $[0;1]$ , sum for each ind. is 1
- Extended in 1999 for either binary or categorical outcomes for survival analysis

- When using censored data, we re-weight the censored information
- rare events problematic (need to research)
- uni-dimensional predictions the same as the mean squared error

## Kattan and Gerds 2018 Use and Misuse of the ROC curve

### Background- C-index

- Due to interpretability desired by clinicians, concordance statistics such as Harrell's c-index, and ROC curve found popularity
- Interpretable for pairs of subjects, but seldom interest to counsel pair of patients
- Only accounts for discrimination and not calibration
- For modeler good to have measure that isolates discrimination, however isolation requires that calibration also be assessed for a comprehensive performance analysis
- Don't separate between useless and harmful model
- They suggest that one would assume a harmful model (incorrectly predicting certainty) having worse score relative to a useless model (a model always predicting prevalence) that predicts with some level of predictive ability
- Further Harrell's c index does not provide a value specific to the time of the horizon of prediction
- This paper suggests that performance prediction ought to be specific to the time horizon of the prediction

### Background-Brier Score

- Overcomes limitations by distinguishing useless from harmless models
- Brier score reflects calibration and discrimination
- Estimated specifically for time horizon
- **BUT:** less interpretable because requires that the performance of model is compared to the performance of the best of the useless models
- Data dependence of reference value complicates Brier Score interpretation
- useless benchmark depends on overall event risk

### Conclusion

- Suggests that one limitation of (index of prediction accuracy; aka calibrated brier score) IPA is that measure using average performance may not reflect improvements that affect a small subset of the population.
- Competing risks are mentioned; claim that two patients may have different clinical decisions even when exact same predicted risk of particular event (competing risks)

# Gerds, T. A., & Schumacher, M. (2006). Consistent estimation of the expected Brier score in general survival models with right-censored event times

## Introduction

- Traditionally, statisticians quantify how close prediction is to the actual outcome, using the R squared and the Brier score.
- Calibration can be measured by e.g. Hosmer Lemeshow “goodness of fit” test.
- Discrimination can be quantified (do patients who have outcome have higher risk predictions than those who dont) using measures such as sensitivtiy , specificity, and area under the ROC (or concordance statistic)
- New methods to assess prediction have gained attention such as reclassification tables, net reclassification improvement (NRI), integrated discrimination improvement (IDI), decision curves based on decision analytic measures( due to novelty not as applied and as common.

## Conclusion

# Nancy R Cook 2007, Use and Misuse of the Receiver Operating Characteristic Curve in Risk Prediction

## Introduction

- Accuracy of models can be assessed via calibration and discrimination.
- **Calibration:** Measure how well predicted probabilities agree with actual observed risk. (prediction develop disease vs actual actual of disease)
- **Discrimination:** Measure of how well model can separate those who do and do not have disease of interest.(when predicts values for cases are all higher than for non-cases, we have perfect discrimination even when predicted risk does not match the proportion with disease)
- Discrimination is more interesting when we have a classification problem with patients that have and dont have prevalent disease (e.g. diagnostic testing).
- Discrimination is measured by c-statistics/ROC
- But when dealing with predictive/prognostic modeling, we need measures that calibrate and discriminate such as the brier score/ $R^2$  and likelihood statistics.
- **Problem:** Risk prediction models in cardiovascular literature, use c-statistic, despite working with large prospective cohort studies.

## ROC Curve and c Statistic

- c- index is the generalization of the ROC for survival data.
- sensitivity of a test is the probability of a positive test result, or the value above a threshold among those with diseases.
- Specificity is the probability of a negative test result, or a value below a threshold among those without disease
- Sensitivity and specificity can be influenced e.g.
- sensitivity among milder cases of disease
- specificity can depend on characteristics of non-cases, e.g. gender, age or prevalence of concomitant risk factors

- ROC is a plot of sensitivity versus 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 noncase.
- Further, c-statistic describes how well models rank case and noncase; but not a function of actual predicted probabilities

### c statistics and Model Selection

- Because c stat is based on ranks it is less sensitive than e.g. measures based on likelihood

## Antolini et al. 2005 A time-dependent discrimination index for survival data

### Introduction

- Extension ROC for censored data, with its biggest advantage being the interpretability
- Suggest time dependent discrimination index
- Ability to discriminate is summarized over time
- Prediction is focused on the individual outcome hence argue focus on accuracy of the predictions, rather than merely on the covariate effects and their statistical significance
- Argue that **generalizability** is important and contains two levels:
  - reproducibility: Patients from same population
  - transportability: Patients coming from different plausibly related population
- Assessing predictive accuracy naively model lead to overoptimistic result
- The evaluation of the degree of optimism and subsequent bias corrected predictive accuracy offers insights into true model reproducibility
- Focus on discrimination (see 7;8 & 9 )
- c-index is discrimination measure introduced by Harrell et al. which is extension of AUC
- AUC is considered the concordance of the ranking between the predicted probabilities of being diseased for pairs of diseased and non-diseased subjects.
- c-index is concordance between ranking of predicted failure times and that of the observed times for pairs of subjects
- Generally speaking, if there is a one to one correspondence between predicted times and predicted survival functions, the ranking between predicted times can be obtained by opposite ranking of predicted survival prob at any fixed time point
- Using non-proportional hazard model for breast cancer patients

### Conclusion

- The core of model development is developing suitable outcome prediction, given the availability of appropriate measures of model predictive accuracy, to evaluate the generalizability to new patients of different prognostic models or to judge the relevance of additional contributions of new covariates.
- Discrimination measure that is established is the ROC and the c-index is an extension for right censored survival data (subject leaves study before event occurs or ends before event happens),

considering the presence of censoring as a population feature rather than a limitation of the sample

- Grounded in following assumption: A subject who developed event should have less predicted probability of surviving beyond his survival time than any subject who survived longer
- Argue that need separate evaluation for prognostic models

## Uno et al 2011 On the C-statistics for Evaluating Overall Adequacy of Risk Prediction Procedures with Censored Survival Data

### Introduction

- Risk score system needed for survival analysis
- Key component is distinguishing between subjects that develop event (cases e.g. death in many survival studies) and subjects that do not (control group)
- For binary outcomes(survival/death) ROC (Receiver Operating Characteristics curve) or area under curve (AUC) have been developed
- Authors call these methods c-statistic
- Estimation based on cond. probability for any pair of “case” & “control” the predicted risk
- When response variable is time, we can use above
- If not interested in time point, standard concordance measure used to evaluate overall performance of scoring system
- Vaguely speaking, one can distinguish between methods that use loss functions (between risk score and survival time) and other based on rank correlations between these variables
- C-statistic by Harell at its core is a rank correlation measure, using Kendall’s tau for censored surv. data
- Problem with rank correlation: **how to order survival times in the presence of censoring**
- Brown et al.: all observations, giving prob. scores based on Kaplan Meier estimate for T
- Problem: KM not good when **covariates dependent on T**
- Alternative: “usable pairs”, excluding rest- Problem: **Dependency on censoring distribution**
- Solution : **modified c-statistic which is consistent for population concordance measure, free of censoring**

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.

### Introduction

- The task of diagnostic and prognostic constitute similar challenges
- The clinician has some information and wants to know how this relates to true patient state currently(diagnostic) or in the future (prognostic)
- Traditional to evaluate statistical prediction we can quantify explained variation via R squared or brier score
- Calibration can be quantified via Hosmer Lemeshow goodness of fit test

- Discrimination can be quantified via measure of sensitivity and specificity via concordance statistics
- New measures include reclassification tables, re-classification improvement and integrated discrimination improvement
- The concept of risk re-classification has caused substantial discussion in methodology and clinical literature
- Decision analytics tools have also found audience for studies focusing on clinical usefulness

### **Predictions models in medicine**

- Model extension with a marker: key interest of clinicians is whether to add a marker to an existing model
- Problem: Overoptimistic weight on marker performance
- Only interested in the incremental added value of the marker
- Usefulness: For a model to be useful it has to be well calibrated
- Decision support important

### **Traditional performance measures**

- Difference between goodness of fit and predictive performance is evaluation on same data while latter requires new data or cordds validation
- **Brier Score**: Quadratic scoring rule, where squared differences between actual binary outcome  $Y$  and prediction  $\hat{r}$  are calculated
- model ranges from 0 to 0.25 for a non-informative model with a 50% incidence of the outcome
- For survival data we used weight function, considering conditional probability of being uncensored during time
- Calculate brier score at fixed time points and create time dependent curve
- Score measures discrimination and calibration each which can be assessed separately

### **Discrimination**

- Concordance statistic is most used for discrimination measure with generalized linear regression models.
- As a rank order statistic, \*\* it is insensitive to systemic errors in calibration such as differences in average outcome\*\*
- popular extension: c statistic with censored data can be obtained by ignoring the pairs that cannot be ordered
- Gonen und Heller propose method where c statistic is independent of censoring
- Time dependent c-statistics have proposed (see above)
- Could also use the discrimination slope to see how well subject with and without outcome are separated

### **Calibration**

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**Novel performance measure**

**Conclusion**

**Integrated Area under the Curve**

$$\text{AUC} = \Pr \{z(\mathbf{X}_i) > z(\mathbf{X}_j) \mid D_i = 1 \& D_j = 0\}$$

**Prognostic Index Curve**

**Prediction error Curves**

**Steyerberg, E. W., & Vickers, A. J. (2008). Decision curve analysis: a discussion.**

**Implementation**

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