Avoiding C-hacking when evaluating survival distribution predictions with discrimination measures

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March 10, 2022

Abstract

In this paper we consider how to evaluate survival distribution predictions with measures of discrimination. This is a non-trivial problem as discrimination measures are the most commonly used in survival analysis and yet there is no clear method to derive a risk prediction from a distribution prediction. We survey methods proposed in literature and software and consider their respective advantages and disadvantages. Whilst distributions are frequently evaluated by discrimination measures, we find that the method for doing so is rarely described in the literature and often leads to unfair comparisons. We find that the most robust method of reducing a distribution to a risk is to sum over the predicted cumulative hazard. We recommend that machine learning survival analysis software implements clear transformations between distribution and risk predictions in order to allow more transparent and accessible model evaluation. The code used in the final experiment is available at https://github.com/RaphaelS1/distribution_discrimination.

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1 Introduction

Predictive survival models estimate the distribution of the time until an event of interest takes place. This prediction may be presented in one of three ways, as a: i) time-to-event, \( Y \in \mathbb{R}_{>0} \), which represents the time until the event takes place; ii) a relative risk, \( \phi \in \mathbb{R} \), which represents the risk of the event taking place compared to other subjects in the same sample; or iii) the probability distribution for the time to the event, \( S \in \text{Distr}(\mathbb{R}_{>0}) \), where \( \text{Distr}(\mathbb{R}_{>0}) \) is the set of distributions over \( \mathbb{R}_{>0} \). Less abstractly, consider the Cox PH \cite{Cox1972}: \( h(t) = h_0(t) \exp(X\hat{\beta}) \) where \( h_0 \) is the ‘baseline’ hazard function, \( X \) are covariates, and \( \hat{\beta} \) are coefficients to be estimated. In practice, software fits the model by estimating the coefficients, \( \beta \). Predictions from the fitted model may then either be returned as a relative risk prediction, \( X\beta \) or \( \exp(X\beta) \), or \( h_0 \) is also estimated and a survival distribution is predicted as \( \hat{h}(t) = h_0(t) \exp(X\beta) \).

The Cox PH is a special type of survival model that can naturally return both a survival distribution and a relative risk prediction, however this is not the case for all models. For example, random survival forests \cite{Ishwaran2008} only return distribution predictions by recursively splitting observations into increasingly homogeneous groups and then fitting the Nelson-Aalen estimator in the terminal node.

2 Methods

We consider how discrimination measures are utilised in the literature to evaluate the predictive performance of models that predict survival distributions (Section 2.1), we then review the identified methods (Sections 2.2 and 2.3). To illustrate our findings we provide a worked example in Section 3. The focus in our review is not to compare the (dis)advantages of measures but instead their compatibility. For example, we do not compare if Antolini’s C is ‘better’ than Harrell’s C but instead note that the former requires a distribution prediction and the latter a risk prediction, hence estimated C-statistics cannot be compared between measures as they evaluate separate predictions types (we call such a comparison ‘C-hacking’).

2.1 Literature Review

We first performed a formal literature review using PubMed and then a less formal review from articles and software packages that had been drawn to our attention. The purpose of the review was to determine how model discrimination predictions have historically been evaluated for machine learning models that make distributional predictions.

We searched PubMed for ‘(comparison OR benchmark) AND (“survival analysis” OR ”time-to-event analysis”) AND “machine learning” AND (discrimination OR concordance OR ”C statistic” OR ”c in-
Figure 1: PRISMA diagram for literature review. Inclusion criteria: Articles that compare machine learning survival predictions with measures of discrimination.

dex”). We excluded articles if: i) they did not use measures of discrimination; ii) no machine learning models were included; iii) only risk-prediction models were included; iv) the models did not make survival predictions (e.g. classifiers). We found 22 articles in our initial search, which were reduced to nine after screening, a full PRISMA diagram is provided in Figure 1 the diagram includes nine other records which were identified outside of the search and which are discussed further below.

A total of nine articles were retained for qualitative assessment [Hadanny et al., 2022, Johri et al., 2021, Loureiro et al., 2021, Mosquera Orgueira et al., 2020, Aivaliotis et al., 2021, Kantidakis et al., 2020, Spooner et al., 2020, Crombé et al., 2021, Herrmann et al., 2020]. All of these, without exception, compared risk-predicting Cox-based models (e.g. regularised, boosted, neural adaptations) to random survival forests Ishwaran et al. [2008]. scikit-survival [Pölsterl, 2020], randomForestSRC [Ishwaran and Kogalur, 2018], ranger [Wright and Ziegler, 2017] and mlr [Bischl et al., 2016] were utilised to implement and evaluate the RSFs. RSFs make distributional predictions by ensembling a Nelson-Aalen estimator across bootstrapped models Ishwaran et al. [2008]. Transformation from distribution to risk is handled in randomForestSRC and scikit-survival by taking the sum over the predicted cumulative hazard function for each observation, which is recommended by Ishwaran et al. [2008], we refer to this transformation as ‘expected mortality’ (Section 2.3.3). In contrast, no transformation is provided in ranger, which only returns a distribution prediction, however this is handled in Spooner et al. [2020] by utilising mlr, which provides the same expected mortality transformation.

As well as these articles, we were also aware of the following articles and software that discuss the discrimination of models that make distributional predictions: Kvamme et al. [2019, Lee et al. [2018, Gensheimer and Narasimhan [2019, Kvalman and Borgan [2019, Sonabend et al. [2021, Zhao and Feng [2020, Haider et al. [2020, Mogensen et al. [2014, Schwarzer et al. [2000, Zhao and Feng [2020, Zhong and Tibshirani [2019 (Section 2.3.3), 3) calculating and comparing a summary statistic (e.g. expected survival time) from the predicted distributions Sonabend et al. [2020, Haider et al. [2020 (Section 2.3.2).
These four methods are grouped according to the required measure, i.e.: A) time-dependent discrimination; and B) time-independent discrimination. Discussion follows after defining some useful notation.

In practice, software for time-to-event predictions will usually return a matrix of survival probabilities. Let \([T_0, T_N]\) be the range of observed survival times in a training dataset, let \(M\) be the number of observations in the test dataset and let \(M^* \leq M\) be the number of time-points for which predictions are made, then we predict \(S \in [0, 1]^{M \times M^*}\), which correspond to predictions of individual survival functions, \(S_i(T), T \in T \subseteq [T_0, T_N]\).

2.2 Time-dependent discrimination

Discrimination measures can be computed as the proportion of concordant pairs over comparable pairs. Let \(i \neq j\) be a pair of observations with observed outcomes and predicted risks of \(\{(T_i, \Delta_i, \phi_i), (T_j, \Delta_j, \phi_j)\}\) respectively. Then \((i, j)\) are comparable if \(T_i < T_j \cap \Delta_i\) and the predicted risks are concordant with the outcome times if \(\phi_i > \phi_j\). In this paper we are concerned with how the values of \((\phi_i, \phi_j)\) are calculated.

Time-dependent discrimination measures define concordance over time either by taking \(\phi_i\) to be predicted survival probabilities such as \cite{Antolini2005}, or as predicted linear predictors, such as \cite{Heagerty2000}. \cite{Antolini2005} define a pair of observations as concordant if the predicted survival probabilities are concordant at the shorter outcome time,

\[
P(\hat{S}_i(T_i) < \hat{S}_j(T_j) | T_i < T_j \cap \Delta_i = 1)
\]

In contrast, \cite{Heagerty2000} calculate the AUC by integrating over specificity and sensitivity measures given by

\[
sensitivity(c, t) = P(\phi_i > c | T_i \leq t)
\]

\[
specificity(c, t) = P(\phi_i \leq c | T_i > t)
\]

Various metrics have been based on these ideas and several are implemented in the R package survAUC \cite{Potapov2012}. However, all require a single relative risk predictor, and therefore require some transformation from a survival distribution prediction, and secondly all assume a one-to-one relationship between the predicted value and expected survival times (which is unlikely in complex machine learning models), for example a proportional hazards assumption where the predicted risk is related to the predicted survival distribution by multiplication of a constant \cite{Potapov2012}.

We are unaware of any time-dependent AUC metrics, except for Antolini’s, that evaluates survival time predictions without a further transformation being required. This may explain why Antolini’s C-index is seemingly more popular in the artificial survival network literature \cite{Kvamme2019,Lee2018}.

On the surface, time-dependent discrimination measures are optimal for evaluating distributions by discrimination. However, they are a poor choice for model comparison. Time-dependent measures that evaluate risk predictions (such as Heagerty’s) require a transformation from survival distribution predictions and any such transformation is unlikely to result in the one-to-one mapping required by the measures. In contrast, Antolini’s evaluates the concordance of a distribution, which means that it can only be used to compare the concordance of two models that make distribution predictions, as opposed to, say, one model that predicts distributions (e.g. RSFs) and one that predicts relative risks (e.g. SVMs). The experiment in Section \ref{timeindependent} demonstrates why results from Antolini’s C cannot be simply compared to results from other concordance indices.

2.3 Time-independent discrimination

Time-independent discrimination measures for survival analysis evaluate relative risk predictions by estimating concordance.

Let \(\mathcal{S} \subseteq \text{Distr}(\mathbb{R}_{>0})\) be a convex set of distributions over the positive Reals; then we define a distribution reduction method as any function of the form: \(f : \mathcal{S} \rightarrow \mathbb{R}\), which map a survival distribution prediction, \(\zeta \in \mathcal{S}\), to a single relative risk, \(\phi \in \mathbb{R}\). In the discrete software analogue, we consider functions \(f^* : [0, 1]^{M^*} \rightarrow \mathbb{R}\).

Distribution reduction methods are required to utilise time-independent discrimination measures for models that make distribution predictions. We consider the three from the literature review in turn.
2.3.1 Comparing probabilities

Evaluating discrimination at a given survival time is formally defined by estimating

$$P(\hat{S}_i(t) < \hat{S}_j(t) | T_i < T_j \cap \Delta_i = 1)$$

(4)

for some chosen $t \in \mathbb{R}_{>0}$. The distribution is reduced to a relative risk by evaluating the survival probabilities at a given time-point,

$$\phi := \hat{S}(t')$$

where $\hat{S}$ is the predicted survival function and $t' \in \mathbb{R}_{>0}$. Note the key difference between this method and Antolini’s C is that $t$ can be arbitrarily chosen here, whereas Antolini’s C estimates the concordance at the observed outcome time.

This method assesses how well a model separates patients at a single time-point; it has several problems: 1) it is not ‘proper’ in the sense that the optimal model may not maximise the concordance at $t'$ [Blanche et al., 2019]; 2) it is prone to manipulation as one could select the $t'$ that maximises the C-index for their chosen model (see Section 3); and 3) if predicted survival curves overlap then evaluation at different time-points will lead to contradictory results (as the observed event time will always stay the same). The above issues apply even if evaluated at several time-points.

2.3.2 Distribution summary

The distribution summary statistic method reduces a probability distribution prediction to a summary statistic, most commonly, the mean or median of the distribution, i.e.,

$$P(E[\zeta_i] < E[\zeta_j] | T_i < T_j \cap \Delta_i = 1)$$

(5)

$$P(m(\zeta_i) < m(\zeta_j) | T_i < T_j \cap \Delta_i = 1)$$

(6)

where $m(\zeta_i)$ is the median of distribution $\zeta_i$. In theory, this should provide the most meaningful reduction with a natural interpretation (mean or median survival time), however this is not the case as the presence of censoring means that the predicted survival predictions will usually result in ‘improper predictions’, i.e. the basic properties of the survival function are not satisfied: $\lim_{t \to \infty} S_T(t) \neq 0$. To see why this is the case, note that the majority of survival distribution predictions make use of a discrete estimator such as the Kaplan-Meier estimator, which is defined as follows:

$$\hat{S}(t) = \begin{cases} 
1 & t < t_{(1)} \\
\prod_{i:t_{(i)} \leq t} (1 - d_i/n_i) & t \geq t_{(1)}
\end{cases}$$

(7)

where $d_i, n_i$ are the number of deaths and events (death or censoring) at ordered events times time $t_{(i)}, i = 1, \ldots, n$. By definition of this estimator, unless all observations at risk in the final time-point experience the event ($d_i = n_i$), the predicted survival probability in this last point will be non-zero.

Several methods have been considered to extrapolate predictions to fix this problem, such as dropping the last predicted probability to zero either at or just after the last observed time-point [Sonabend et al., 2021], or by linear extrapolation from the observed range [Haider et al., 2020] (Figure 2). However these methods require unjustifiable assumptions and result in misleading quantities. For example, dropping the survival probability to zero immediately after the study end assumes that all patients (no matter their risk) instantaneously die at the same time, which will skew the distribution mean and median towards the final event time [Haider et al., 2020]. The extrapolation method has the opposite problem, if the prediction survival curves are shallow then the extrapolated predictions can easily result in impossible (or at least highly unrealistic) values (Figure 2).

However, we note that summarising a ‘proper’ distribution prediction (i.e. one that doesn’t violate the limit properties) by its mean or median will provide a natural relative risk. But this is rarely the case for all predicted distributions in a test set and so the problem remains.

2.3.3 Expected mortality

The final time-dependent discrimination method estimates

$$P(\phi_i > \phi_j | T_i < T_j \cap \Delta_i = 1)$$

(8)

where

$$\phi_i := \sum_{t \in \mathcal{T}} - \log \hat{S}_i(t) = \sum_{t \in \mathcal{T}} \hat{H}_i(t)$$

(9)
Figure 2: Extrapolation methods to ‘fix’ improper distribution predictions. Top: Kaplan-Meier estimator fit on the rats [Therneau, 2015] dataset, which results in an improper distribution as $\lim_{T \to \infty} = 0.81 \neq 0$. Middle: Dropping the survival probability to zero at $T = 105$, just after the study end. Bottom: Dropping the survival probability to zero by linearly extrapolating from first, $(S(T) = 1, T = 0)$, and last, $(S(T) = 0.81, T = 104)$, observed survival times. Dashed horizontal lines are drawn at $S(T) = 0.5$ and dotted vertical lines at $T = 104$, where the observed data ends and the extrapolation begins. Median ($m$) and mean ($\mu$) are provided for both extrapolation methods. Both methods result in quantities skewed heavily toward the final extrapolated time. For the ‘dropping’ method the median is exactly at the final time. Linear extrapolation results in probabilities that are unrealistically large.
and $\hat{H}_i, \hat{S}_i$ are the predicted cumulative hazard and survival functions respectively. Summing over the predicted cumulative hazard provides a measure of expected mortality for similar individuals [Hosmer Jr et al., 2011, Ishwaran et al., 2008] and a closely related quantity can even be used as measure of calibration [Van Houwelingen, 2000].

The advantage of this method is that it requires no model assumptions, nor assumptions about the survival distribution before or after the observed time period, and finally, the reduction method provides an interpretable quantity that is meaningful as a relative risk: the higher the expected mortality, the greater the risk of the event.

3 Motivating Example

We now present a motivating example to make clear why these different concordance measures cannot be directly compared in model evaluation and why it is important to be precise about which method is utilised in model comparison studies.

Experiment Design  We split the rats dataset from R package survival [Therneau, 2015] into a random holdout split with 2/3 of the dataset for training and 1/3 for testing; a seed was set for reproducibility. With the training data we fit a Cox PH (CPH) with package survival, random survival forest (RSF) with package ranger, and gradient boosting machine with C-index optimisation (GBM) [Mayr and Schmid, 2014] with package mboost [Hothorn et al., 2020]. Note that ranger only returns distribution predictions for RSFs and mboost only returns risk predictions.

Evaluation Measures  We used each model to make predictions on the holdout data. For the Cox PH we made linear predictor predictions with survival::coxph and additionally distribution predictions with survival::survfit. We evaluate the discrimination of all possible predictions with: Harrell’s C, $C_H$, [Harrell et al., 1982] (‘Harrell’) on the native risk prediction (i.e. returned by package without further user transformation), Uno’s C [Uno et al., 2011] (‘Uno’) on the native risk prediction, Antolini’s C [Antolini et al., 2005] (‘Antolini’), $C_H$ computed on the survival probabilities at every predicted time-point, $C_H$ computed on the distribution mean without any extrapolation (‘Summary (naive)’), $C_H$ computed on the distribution mean with extrapolation method of dropping to zero just after the final time point (‘Summary (extr)’), and $C_H$ computed on the expected mortality (‘ExpMort’). For reporting the concordance computed on survival probabilities at each time-point, we reported the time-point which resulted in the maximum $C_H$ for the RSF, the time-point that resulted in the minimum $C_H$ for the RSF, and one randomly sampled time-point. Note that ‘Harrell’ and ‘Uno’ in Table 1 cannot be computed for RSF, which does not return a native risk prediction. Similarly, for the GBM only ‘Harrell’ and ‘Uno’ can be computed as all other methods require a distribution prediction, which does not exist for C-index boosted GBMs.

Results  The results (Table 1) indicate how ranking the performance of different algorithms changes depending on the C-index used. The following are examples for how the results in the table could be reported (from most transparent to least):

1. CPH is the best performing for distribution predictions under Antolini’s $C$ with a C-index of 0.852 compared to RSF’s 0.757
2. RSF is the best performing for distribution predictions under the expected mortality transformation with Harrell’s $C$ with a C-index of 0.878 compared to CPH’s 0.859.
3. CPH is the best performing for risk predictions under Uno’s C with a C-index of 0.861 compared to GBM’s 0.853
4. RSF is the best performing model with a C-index of 0.897, then CPH with C-index of 0.861 and then GBM with C-index of 0.853.

The first three of these are the clearest as they demonstrate what is being evaluated and how. However, the difference between the first two demonstrates how the result can be chosen by the researcher by selecting one measure over another. The final is clearly the least transparent as it mixes many types of predicted types and evaluation measures to draw conclusions.
**Discussion**  These examples demonstrate how simply reporting "the C-index" without being more precise can lead to manipulation of results (deliberate or otherwise). For example, the absurdly low values for ‘Summary (naive)’ are a result of attempting to calculate the distribution mean from improper distribution predictions, which is easily possible with *lifelines* [Davidson-Pilon 2019] and *mlr3proba* [Sonabend et al. 2021] (the latter has since been updated in light of this problem). Similarly, despite providing a warning in documentation and on usage, *pec* [Mogensen et al., 2014] still allows concordance evaluation at arbitrary survival points, which could lead to authors reporting the maximum C-index over all time-points ('Prob (max)’ in Table 1).

It is clear that a shift in reporting is required. When a range of C-indices are tabulated as in Table 1 then dishonest reporting (like the final example above) is clear however in practice a range of values is not reported and instead just a vague ‘C-index’. This problem is analogous to any statistical manipulation, for example p-hacking. The methods of dealing with the problem, ‘C-hacking’, are therefore also the same. Researchers should either: 1) decide at the beginning of an experiment what method they will use for evaluating concordance and state this clearly; or 2) report a wide range of methods depending on utilised software.

| Method       | CPH  | RSF  | GBM  |
|--------------|------|------|------|
| Harrell      | 0.859| –    | 0.831|
| Uno          | **0.861** | –    | **0.853** |
| Antolini     | 0.852| 0.757| –    |
| Prob (min)   | 0.500| 0.500| –    |
| Prob (max)   | 0.859| **0.897** | –    |
| Prob (rand)  | 0.859| 0.851| –    |
| Summary (naive) | 0.141| 0.104| –    |
| Summary (extr) | 0.859| 0.871| –    |
| ExpMort      | 0.859| 0.878| –    |

Table 1: Various C-index calculations from different methods and models. Included models are Cox PH (CPH), random survival forest (RSF) and gradient boosting machine with C-index optimisation (CPH). Methods of evaluation are: Harrell’s C ($C_H$) on native risk predictions (i.e. predictions from software without further transformation) (‘Harrell’), Uno’s C on native risk predictions (‘Uno’), Antolini’s C on distribution predictions (‘Antolini’), $C_H$ computed on the predicted survival probability at the time-point that results in the smallest value for RSF (‘Prob (min)’), $C_H$ computed on the predicted survival probability at the time-point that results in the largest value for RSF (‘Prob (max)’), $C_H$ computed on the predicted survival probability at an arbitrary time-point (‘Prob (rand)’), $C_H$ computed on the distribution expectation without any extrapolation (‘Summary (naive)’), $C_H$ computed on the distribution expectation after extrapolating by dropping survival probabilities to zero (Fig 2 middle) (‘Summary (extr)’), $C_H$ computed on the expected mortality (‘ExpMort’). Empty values indicate that the given method is incompatible with the resulting predictions. Values in bold are the maximum C-index for that model.

4 Conclusions

In this paper, we reviewed the literature for different methods of evaluating survival distribution predictions with methods of concordance. For time-dependent measures, only Antolini’s C can be directly applied to distribution predictions. This measure can be utilised to compare the discrimination of multiple models that make distribution predictions however as it cannot be applied to models that make risk predictions, its use in benchmark experiments is more limited. In contrast, methods that reduce a distribution prediction to a risk prediction allow for time-independent discrimination measures to be utilised for any combination of survival models. Of the reviewed ‘distribution reduction’ methods that we found in the literature, the expected mortality method of summing over the cumulative hazard was the most robust as it requires no assumptions about the model or prediction and is therefore applicable to all distribution predictions. Once the distribution is reduced to a risk, any time-independent discrimination measure can be applied (e.g. Harrell’s C).

Our motivating example demonstrates why understanding the differences between these methods is so important and how an imprecise statement of methods can lead to simple manipulation of results. We
believe this is an important change that must be made from the top-down to ensure it is quickly adopted. Journals should require clear reporting on how c-statistics are computed in survival analysis to ensure fair reporting of results and to avoid ‘C-hacking’. Furthermore, all open-source software should provide methods to transform distribution to risk predictions, such as the compositions in Sonabend et al. [2021].

In general, researchers should make use of a wide range of evaluation metrics including measures of calibration as well as scoring rules. Whichever metrics are chosen, researchers should be precise about exactly which estimators are utilised and any post-processing of results that was required.

Competing interests
There is NO Competing Interest.

Author contributions statement
RS conceptualised the article. All authors contributed equally to writing and editing.

Funding
AB has been funded by the German Federal Ministry of Education and Research (BMBF) under Grant No. 01IS18036A. The authors of this work take full responsibilities for its content.

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