

# Quantifying predictive accuracy in Cox models

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# Introduction

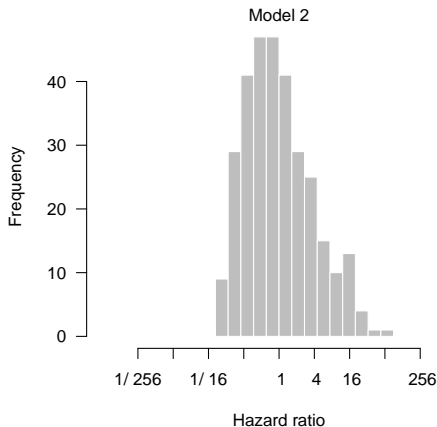
- Today's lecture will address the question: Overall, how well can a given model predict survival?
- To illustrate, we'll look at three models for the cirrhosis data:
  - Model 1:  $\text{trt} + \text{albumin}$
  - Model 2:  $\text{trt} + \text{stage} + \text{hepato} + f(\text{albumin}) + \log(\text{bili})$
  - Model 3: Model 2 + 30 variables of random noise
- The idea here is to see how various metrics compare when applied to a model with decent predictive ability (model 1), a model with very good predictive ability (model 2), and a model in which overfitting is present (model 3)

# Linear predictors

- One simple approach to describing the amount of signal present in a model is to describe the linear predictors
- Hazard ratios are direct functions of the linear predictors, so by inspecting the distribution of linear predictors, we get a sense of the extent to which our model can identify individuals as high risk and low risk, as opposed to saying that everyone has about the same risk
- For our three models:
  - Model 1:  $SD(\hat{\eta}) = 0.70$
  - Model 2:  $SD(\hat{\eta}) = 1.31$
  - Model 3:  $SD(\hat{\eta}) = 1.75$

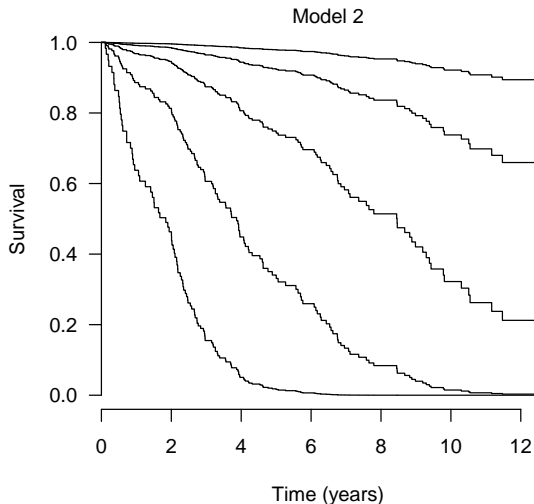
# Histograms

Plotting the distribution makes the same point, but also illustrates the distribution of values:



# Survival plots

A related idea is to plot the baseline hazard  $\pm 1$  and 2 SDs:



## Introduction: $R^2$

- It is typically desirable to be able to summarize these illustrations into a single number that quantifies a model's accuracy
- For example, in linear regression we have  $R^2$ , the proportion of variance in the outcome explained by the model
- Many authors have proposed various ways of constructing a measure like  $R^2$  for Cox regression; the motivations typically proceed by analogy

# Derivation

- One widely used  $R^2$  measure for Cox regression is based on the likelihood ratio test statistic:

$$\text{LR} = 2(\ell_1 - \ell_0),$$

where  $\ell_1$  is the log-likelihood of the fitted model and  $\ell_0$  is the log-likelihood for the null model

- For linear regression, we have

$$R^2 = 1 - \frac{\text{RSS}_1}{\text{RSS}_0},$$

where  $\text{RSS}_1$  and  $\text{RSS}_0$  are the residual sums of squares for the fitted and null models

- For linear regression, we also have

$$\text{LR} = n \log \frac{\text{RSS}_0}{\text{RSS}_1}$$

## Likelihood ratio $R^2$

- This suggests

$$R^2 = 1 - \exp(-\text{LR}/n)$$

as a way of calculating an  $R^2$  for Cox models; note that  $n$  here is the number of observations, not the number of events

- For our three models:
  - Model 1:  $R^2 = 0.18$
  - Model 2:  $R^2 = 0.45$
  - Model 3:  $R^2 = 0.55$
- This has essentially the same interpretation as  $R^2$  in linear regression, although one may certainly question how appropriate the analogy is
- $R^2$  is reported by `summary(fit)` in the `survival` package



## Concordance: Introduction

- An alternative idea is to quantify a model's accuracy on the basis of concordance
- The idea here is to consider all possible pairs of observations and sort them into concordant and discordant groups based on their outcomes and the model's predictions

## Concordant pairs

- For example, suppose we observe a pair with  $t_i = 100, d_i = 1, \eta_i = 1$  and  $t_j = 150, d_j = 1, \eta_j = 0$
- This is a *concordant* pair, in that the model predicts that subject  $i$  will die first, and this coincides with what actually happened
- Note that we can still have concordant pairs in the presence of censoring:  $t_i = 100, d_i = 1, \eta_i = 1$  and  $t_j = 150, d_j = 0, \eta_j = 0$  also form a concordant pair

## Discordant and indeterminate pairs

- Conversely,  $t_i = 100, d_i = 1, \eta_i = 0$  and  $t_j = 150, d_j = 1, \eta_j = 1$  would be a *discordant pair*: we predict that subject  $j$  is higher risk, but they in fact survive longer than subject  $i$
- Not all pairs can be classified as concordant or discordant, however; in the presence of censoring, pairs can also be indeterminate
- For example, suppose we observe  $t_i = 100, d_i = 0, \eta_i = 1$  and  $t_j = 150, d_j = 1, \eta_j = 0$
- We predict that subject  $i$  dies first, but we have no way of knowing whether that actually happened

# Scoring

- Finally, we can also have tied pairs, either because the predictors are tied ( $\eta_i = \eta_j$ ) or because the failure times are tied ( $t_i = t_j$ , with  $d_i = d_j = 1$ )
- In aggregating the results, the model scores one point for every concordant pair and half a point for every tied pair
- This score is then divided by the total number of non-indeterminate pairs to obtain a *concordance index*
- As a formula,

$$C = \frac{n_c + 0.5n_t}{n_c + n_d + n_t},$$

where  $n_c$  is the number of concordant pairs,  $n_d$  is the number of discordant pairs, and  $n_t$  is the number of tied pairs

## Example: Model 2

- For example, in the pbc data, there are 312 observations, so  $\binom{312}{2} = 48,516$  pairs
- For model 2, those pairs fall into the following categories:
  - 23,653 were concordant
  - 5,061 were discordant
  - 17 were tied
  - 19,785 were indeterminate
- This gives  $C = 0.82$
- In the pbc data, 14% of the observations are censored, resulting in 41% of the pairs being indeterminate; to contrast, in the VA lung data, only 7% of the observations are censored, and only 5% of the pairs are indeterminate

## Concordance results

- By construction,  $C$  must be between 0 and 1, with 1 representing perfect agreement between model and observation and 0.5 representing random guesses
- In survival data,  $C = 0.6 - 0.8$  is pretty common
- For our three models,
  - Model 1:  $C = 0.69$
  - Model 2:  $C = 0.82$
  - Model 3:  $C = 0.85$
- $C$  is reported by `summary(fit)` along with  $R^2$ ; you can also obtain a more detailed report from `survConcordance`

# Overfitting

- You have probably noticed that for all of these measures, model 2 is more accurate than model 1 (this is likely genuine) and model 3 is more accurate than model 2 (this is not genuine, as model 3 is just model 2 plus junk)
- This is because none of the methods we have discussed so far address overfitting in any way
- All of these measures describe how well the model agrees with the already observed outcomes; this is not really what we want to know
- What we really want to know is how accurate the model is at *predicting* future observations

# Optimism

- Measures of accuracy are almost always better for already observed outcomes than they are for future predictions, because the observed outcomes were used to build the model in the first place
- To be more precise, let  $M$  denote a generic measure of accuracy,  $\mathbf{y}$  denote the observed outcomes (for survival, this includes  $t$  and  $d$ ),  $\mathbf{y}^*$  denote future outcomes, and  $f(\mathbf{X})$  denote a model's predictions
- Because of this phenomenon of overfitting, the quantity

$$M\{f(\mathbf{X}), \mathbf{y}\} - M\{f(\mathbf{X}), \mathbf{y}^*\}$$

is almost always positive; this quantity is known as the *optimism* of the model, and it tends to be more severe for complex models than simple models



# Shrinkage

- Unfortunately, methods for estimating optimism are underdeveloped in survival analysis, at least with respect to other regression models
- However, one useful approach is the shrinkage heuristic developed by van Houwelingen and le Cessie (1990)
- Those authors developed the estimator for the shrinkage coefficient,  $\gamma$ :

$$\hat{\gamma} = 1 - \frac{df}{LR},$$

where  $df$  denotes the degrees of freedom of the model

# Calibration

- The idea is that the model's predictions,  $\{\hat{\eta}_i\}$ , should be shrunk towards zero by  $\gamma$ :

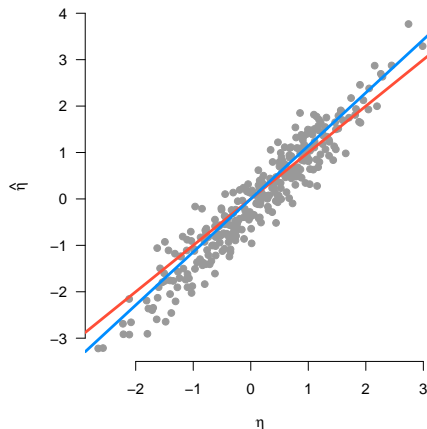
$$\tilde{\eta}_i = \hat{\gamma} \eta_i$$

- This is referred to as *calibration*; the idea is that the model's predictions need to be re-calibrated in order to account for the inevitable optimism that any model possesses
- Remark: This is not the only way to estimate  $\gamma$ ; for example, a few authors have proposed estimators based on bootstrapping

# Simulation

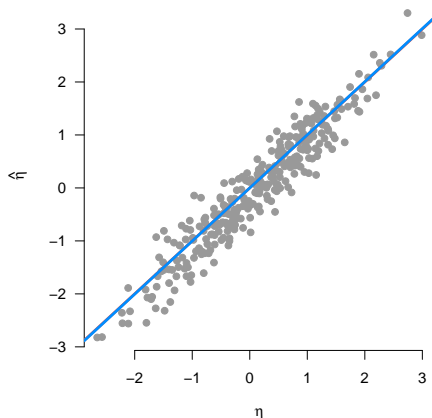
- To illustrate how this works, let's simulate some survival data from an exponential model (for simplicity, all observations are uncensored)
- In the generating model, there are 2 predictors for which a 1 SD change yields a hazard ratio of 2, and 28 predictors that have no effect on hazard
- Since this is simulated data, we can check the agreement between  $\{\hat{\eta}_i\}$  and the true  $\{\eta_i\}$  values for both the original and shrunk (calibrated) versions (in this example,  $\hat{\gamma} = 0.87$ )

# Original estimates



Red: 1-to-1 line; blue: least squares line

## Calibrated estimates



Red: 1-to-1 line; blue: least squares line

# Calibration results

- For our models:
  - Model 1:  $\hat{\gamma} = 0.97$
  - Model 2:  $\hat{\gamma} = 0.97$
  - Model 3:  $\hat{\gamma} = 0.86$
- This makes sense: models 1 and 2 are fairly parsimonious, and we shouldn't have to shrink their estimates much, while model 3 deserves some shrinkage
- The calibrated versions of  $SD(\eta)$ :
  - Model 1:  $SD(\tilde{\eta}) = 0.68$
  - Model 2:  $SD(\tilde{\eta}) = 1.28$
  - Model 3:  $SD(\tilde{\eta}) = 1.50$

## Calibrated $R^2$ ?

- It would seem like a reasonable idea to use  $\hat{\gamma}$  to obtain calibrated versions of  $R^2$  and  $C$  as well (e.g.,  $\tilde{R}^2 = \hat{\gamma}R^2$ ):
  - Model 1:  $\tilde{R}^2 = 0.17$
  - Model 2:  $\tilde{R}^2 = 0.44$
  - Model 3:  $\tilde{R}^2 = 0.47$
  - Model 1:  $\tilde{C} = 0.69$
  - Model 2:  $\tilde{C} = 0.81$
  - Model 3:  $\tilde{C} = 0.80$
- I don't think I've ever actually seen anyone report this in an article, but it seems like a reasonable idea, at least to me...

## Final remarks

- As I said, methods for addressing optimism and overfitting in Cox models are relatively underdeveloped, so many questions are unresolved
- In part, this is due to inherent challenges in evaluating the absolute accuracy of predictions for a model that only estimates *relative* risks
- For example, cross-validation is a widely used technique for evaluating the predictive accuracy of models while properly accounting for overfitting/optimism
- But how exactly should we carry out cross-validation for a Cox model?



## Final remarks (cont'd)

- For example, we can fit the data to  $\{\mathbf{X}, \mathbf{t}, \mathbf{d}\}_{-i}$  and calculate the linear predictor  $\hat{\eta}_i = \mathbf{x}_i^T \hat{\boldsymbol{\beta}}$ , but that linear predictor quantifies risk relative to the observations in  $\{\mathbf{X}, \mathbf{t}, \mathbf{d}\}_{-i}$ . . . upon observing  $t_i$  and  $d_i$ , how do we evaluate whether this was a good prediction or not?
- We can't use the Cox partial likelihood: with only one observation in the risk set, the likelihood would be 1 regardless of  $\hat{\eta}_i$
- This is not to say that there are no solutions proposed in the literature, rather just to re-emphasize that it's a challenging issue and worth further research