Cox regression: Inference

Patrick Breheny

October 25

Introduction

- Today we will discuss inference for the Cox model; this discussion will be brief, as all of our previous likelihood-based methods apply to the Cox partial likelihood
- We will also formally introduce `coxph`, the function in the `survival` package that fits Cox proportional hazards models
- Finally, we will take a look at how the results from the Cox model applied to several our example data sets compare to the results we obtained from parametric models

Wald inference

- Just as in the case of parametric inference, Wald-based inference is based off of the asymptotic result

  $$\widehat{\boldsymbol{\beta}} \dot{\sim} \mathrm{N}(\boldsymbol{\beta}, (\mathbf{X}^T\mathbf{W}\mathbf{X})^{-1}),$$

  where expressions for the elements of $\mathbf{W}$ were derived in the previous lecture
- The composition of $\mathbf{W}$ is of course very different for Cox regression than what we had in the exponential regression case, but all formulas and procedures remain the same
- In particular, $100(1-\alpha)\%$ confidence intervals are constructed via $\widehat{\beta}_j \pm z_{(\alpha/2)}\sqrt{(\mathbf{I}^{-1})_{jj}}$

Likelihood ratio confidence intervals

- As we saw with parametric models, likelihood ratio methods are typically the most accurate of the asymptotic likelihood approaches
- However, they are somewhat cumbersome for the purposes of constructing confidence intervals, as they require profiling
- For this reason, likelihood ratio confidence intervals are rare in practice

Likelihood ratio tests

- Likelihood ratio tests, however, are common and widely used, especially when comparing nested models that differ with respect to multiple parameters
- For example, in the pbc data, suppose we wished to compare the fit of a linear effect for stage versus the fit allowing separate parameters describing the relative risk of each stage
- Letting $\widehat{\boldsymbol{\beta}}_0$ denote the fit of the first model and $\widehat{\boldsymbol{\beta}}_1$ denote the fit of the second model, the likelihood ratio test (which only requires fitting two models) is based on

$$2\{\ell(\widehat{\boldsymbol{\beta}}_1) - \ell(\widehat{\boldsymbol{\beta}}_0)\} \,\dot{\sim}\, \chi^2_2;$$

3 parameters for the four stages minus a single parameter assuming linearity = 2 df

Score tests

- The score, like the likelihood ratio, requires profiling in order to construct confidence intervals and is thus rarely used for this purpose in practice
- Score tests for Cox regression are not particularly common either; however, they do have the advantage, as you hopefully saw in the current assignment, that the significance of adding new terms to a model can be tested without actually fitting any new models
- Nevertheless, there is an interesting connection between the score test in a Cox model and the log-rank test that is worth discussing

Score and log-rank tests

- Consider the Cox regression score test in the special case with only one covariate, an indicator function
- In that case, the Cox score statistic for testing $H_0 : \beta = 0$ is

$$\begin{aligned} u(0) &= \sum_j (x_j - \mathbb{E}_j x) \\ &= \sum_j \left(d_{1j} - d_j \frac{n_{1j}}{n_j} \right), \end{aligned}$$

  or W from the log-rank test
- Thus, the Cox regression score test is in some sense equivalent to the log-rank test, although the variances are calculated differently and therefore don't produce the exact same p-value

coxph

- The function for fitting Cox proportional hazards models in the `survival` package is called `coxph`
- Broadly speaking, the syntax is similar to other model-fitting functions in R:

```
fit <- coxph(S ~ trt + stage + hepato + bili, pbc)
```

  where `S` is a `Surv` object
- Once we have fit the model, there are a number of functions that can be called on the fitted model object; we will go over most of them now, although some are more complex and we will save for a later time (e.g, `residuals(fit)`)

coef, vcov, and model.matrix

Several functions should be familiar to you from your past experience with modeling functions in R:

- `coef(fit)`: Returns the MLE of the coefficient vector, $\widehat{\boldsymbol{\beta}}$
- `vcov(fit)`: Returns the inverse of the information matrix, $(\mathbf{X}^T\mathbf{W}\mathbf{X})^{-1}$
- `model.matrix(fit)`: Returns the design matrix, $\mathbf{X}$; this is particularly convenient when things like factors, interactions, and basis expansions are present in the model formula

summary

```
> summary(fit)
  n= 312, number of events= 144

            coef exp(coef) se(coef)      z Pr(>|z|)
trt     -0.15473   0.85664  0.16813 -0.920    0.357
stage    0.62138   1.86149  0.12816  4.848 1.24e-06 ***
hepato   0.34854   1.41700  0.21269  1.639    0.101
bili     0.13353   1.14285  0.01392  9.591  < 2e-16 ***

       exp(coef) exp(-coef) lower .95 upper .95
trt       0.8566     1.1673    0.6162     1.191
stage     1.8615     0.5372    1.4480     2.393
hepato    1.4170     0.7057    0.9340     2.150
bili      1.1429     0.8750    1.1121     1.174


...
```

summary

```
> summary(fit)

...

Concordance= 0.797  (se = 0.026 )
Rsquare= 0.348   (max possible= 0.991 )
Likelihood ratio test= 133.3  on 4 df,   p=0
Wald test            = 154  on 4 df,   p=0
Score (logrank) test = 212.1  on 4 df,   p=0
```

- We will discuss concordance and R^2 in a future lecture
- The Wald, Score, and LRT tests here are testing the global hypothesis $H_0 : \beta_1 = \beta_2 = \beta_3 = \beta_4 = 0$

anova

- Earlier, we proposed the idea of a likelihood ratio test for whether a linear effect for stage was adequate, or whether a three parameter representation would offer a better fit
- This can be carried out using the anova function:

```
> fit0 <- coxph(S ~ trt + hepato + bili + stage, pbc)
> fit1 <- coxph(S ~ trt + hepato + bili +
                  factor(stage), pbc)
> anova(fit0, fit1)
Analysis of Deviance Table
 Cox model: response is  Surv(time, status != 0)
 Model 1: ~ trt + stage + hepato + bili
 Model 2: ~ trt + factor(stage) + hepato + bili
   loglik  Chisq Df P(>|Chi|)
1 -672.17
2 -671.34 1.6635  2    0.4353
```

logLik and AIC

- Like many likelihood-based procedures, coxph allows you to extract the (partial) log-likelihood using logLik:

```
> logLik(fit0)
'log Lik.' -672.1719 (df=4)
> logLik(fit1)
'log Lik.' -671.3401 (df=6)
```

- This, in turn, means that other functions that depend on log-likelihoods, such as AIC, can be called:

```
> AIC(fit0)
[1] 1352.344
> AIC(fit1)
[1] 1354.68
```

BIC

- Same with BIC:

```
> BIC(fit0)
[1] 1364.223
> BIC(fit1)
[1] 1372.499
```

- However, note that this BIC calculation uses the formula

$$\mathrm{BIC} = -2\ell + \log(d)\mathrm{df},$$

  with d, the number of *events*, replacing n

- This is supported by a paper from by Volinsky & Raftery (2000) showing that this yielded more accurate approximations to the true Bayes factors

Predictions

- Like many regression models, `coxph` also provides a `predict` method
- However, this is worth discussing carefully, as Cox regression does not provide true "predictions"
- In particular, the Cox model estimates only the relative risk for each subject compared to an unspecified baseline hazard
- As a consequence, the linear predictors $\{\eta_i\}$ do not have any absolute meaning, in the sense that one could redefine them according to $\{\tilde{\eta}_i = \eta_i + C\}$ for any constant C and the likelihood would remain the same

Invariance

- This is unappealing because it means that if we code, say, treatment as 0/1, as opposed to -1/1 or 1/2, we will get different predicted values for $\{\eta_i\}$
- To resolve this difficulty, standard practice is to center $\mathbf{X}$ prior to fitting so that each column has mean zero
- This does not affect $\widehat{\boldsymbol{\beta}}$ in any way, but it does mean that the linear predictors for Cox regression are invariant to changes of location and scale

predict

- As a concrete example:

```
> new <- data.frame(trt=0, stage=2, hepato=1, bili=1)
> predict(fit, new)
-0.5416297
```

- This is different from

```
> XX <- as.matrix(new)
> XX %*% coef(fit)
1.724818
```

but the same as

```
> m <- apply(model.matrix(fit), 2, mean)
> (XX-m) %*% coef(fit)
-0.5416297
```

PBC data

- We'll now carry out some comparisons between the Cox model and some parametric PH models of estimates and confidence intervals for various data sets
- First, the `stage` coefficient for PBC data:

	$\widehat{\beta}$	Lower	Upper
Cox	0.621	0.370	0.873
Weibull	0.625	0.367	0.884
Exponential	0.564	0.317	0.811

- It is reassuring that Cox agrees with Weibull here, both in terms of estimates and width of confidence intervals, given that our diagnostic plots suggested that the Weibull is a reasonable parametric model for this data

Pike data

- Now for the estimate of pretreatment regimen for the Pike data:

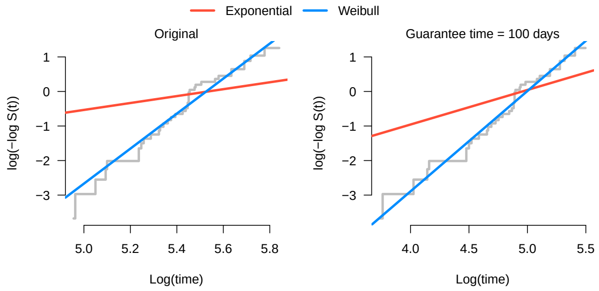
	$\widehat{\beta}$	Lower	Upper
Cox	-0.569	-1.249	0.112
Weibull	-0.720	-1.375	-0.065
Exponential	-0.093	-0.747	0.561

Guarantee time

- Our earlier diagnostic plots suggested that the Weibull was a reasonable model here (certainly much better than the exponential)
- The Weibull may provide a poor fit at earlier times, however, in that no failures occur before day 142
- To account for this, Pike's original analysis modeled time to failure *starting at day 100*
- These first 100 days are known as a *guarantee time*, in the sense that it assumes a guarantee that no rats will die during that time span

Model comparison

- A comparison of the diagnostic plots:



- Log-likelihood provides an objective indication that the guarantee time model fits (slightly) better: $\ell_0 = -193.4$; $\ell_{100} = -191.9$

Pike data; guarantee time = 100 days

Revisiting the Pike data with a guarantee time of 100 days, we find that the Weibull (and exponential) estimates and confidence intervals have moved closer to those of the Cox model

	$\widehat{\beta}$	Lower	Upper
Cox	-0.569	-1.249	0.112
Weibull	-0.660	-1.314	-0.005
Exponential	-0.175	-0.830	0.479

GVHD data

Our final data set for today is the GVHD data:

	$\widehat{\beta}$	Lower	Upper
Cox	-1.152	-2.166	-0.138
Weibull	-1.317	-2.417	-0.216
Exponential	-1.529	-2.541	-0.517

Recall that there is no reason to think that either the Weibull or exponential estimates are particularly accurate here

GVHD data

What about applying an artificial censoring time of 60 days to all subjects still at risk at that time, as we did on assignment 6?

	$\widehat{\beta}$	Lower	Upper
Cox	-1.152	-2.166	-0.138
Weibull	-1.255	-2.361	-0.149
Exponential	-1.238	-2.250	-0.226

Again, the Weibull and exponential results move much closer to the Cox results