# Cox regression: Inference

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# 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 we saw in a previous 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 do no 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

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

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:

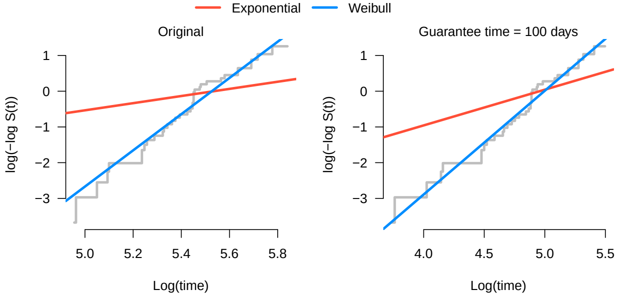
| | $\widehat{\beta}$ | Lower | Upper |
|---|---|---|---|
| Cox | -0.569 | -1.249 | 0.112 |
| Weibull | -0.720 | -1.375 | -0.065 |
| Exponential | -0.093 | -0.747 | 0.561 |

# 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