Implementation of the Proportional Hazards Model
Statistics 255 - Survival Analysis

Presented January 28, 2016
Breast Cancer Survival

Breast Cancer Example - 2 Sample

- 10-year follow up of breast cancer patients (Sedmak el al. Modern Pathology 2 (1989): 516-520)

- Scientific question: How does baseline immunohistochemical (IH) status at diagnosis (2 = positive, 1 = negative) effect survival?

- Available data include:
  - Time to death or on-study time, months
  - Death indicator (0=alive, 1=dead)
  - Immunohistochemical response (1=negative, 2=positive)

- A quick look at the data...
Breast Cancer Example - 2 Sample

- Fit the proportional hazards model to the data...

```r
> fit <- coxph( Surv( time, idead ) ~ ihresp, data=brca )
> summary( fit )
Call:
  coxph(formula = Surv(time, idead) ~ ihresp, data = brca)

  n= 45

  coef  exp(coef) se(coef)      z  Pr(>|z|)
ihresp 0.980   2.665  0.435  2.25  0.024 *

---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1  1

  exp(coef) exp(-coef) lower .95 upper .95
ihresp   2.66     0.375     1.14     6.25

Rsquare= 0.094  (max possible= 0.976 )
Likelihood ratio test= 4.45  on 1 df,  p=0.035
Wald test      = 5.08  on 1 df,  p=0.0242
Score (logrank) test = 5.49  on 1 df,  p=0.0191
```
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Breast Cancer Example - 2 Sample

- Conclusion: estimate of effect of ihresp:
  \[ \hat{\phi} = e^{\hat{\beta}} = 2.66 \Rightarrow \text{the risk of death is 2.66 times higher for the IH-positive group, as compared to the IH-negative group} \]

- Hypothesis tests for effect:
  - Wald’s test of \( H_0 : \beta = 0 \):
    
    Standardize \( \hat{\beta} \) by \( \hat{se}(\hat{\beta}) \) to obtain \( z \)
    
    \[ z = \frac{\hat{\beta}}{\hat{se}(\hat{\beta})} = \frac{.9801995}{.4348896} = 2.254 \]
    
    and thereby obtain a 2-sided \( P \)-value:
    
    \[ P\text{-value} = \Pr\{|Z| \geq z\} = \Pr\{|Z| \geq 2.254\} = 0.024 \]
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Breast Cancer Example - 2 Sample

- 95% Confidence interval for RR: First, a 95% CI for $\beta$:

$$0.980 \pm 1.96 \times 0.435 = 0.980 \pm 0.8526 = [0.1274, 1.8326]$$

exponentiating gives a 95% CI for $\phi = \exp(\beta)$:

$$[e^{0.1274}, e^{1.8326}] = [1.14, 6.25]$$

- This interval does not contain 1, indicating that the effect is significant at the 5% level (consistent with the Wald test)
## Laryngeal Cancer Example - Multiple Regression

**Recall:** If $x$ is an indicator variable (for two sample case), $\log(\beta)$ is the log-relative hazard comparing group 1 ($x = 1$) to group 0 ($x = 0$).

### Example

- Consider the following proportional hazards model for the laryngeal cancer data

\[
\lambda(t) = \lambda_0(t)e^{\beta_1 \text{age}_i + \beta_2 I(\text{stage}_i = 2) + \beta_3 I(\text{stage}_i = 3) + \beta_4 I(\text{stage}_i = 4)}
\]

- What is the interpretation of $\beta_1$?
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Laryngeal Cancer Example - Multiple Regression

Example
Compare a subpopulation of 66 year olds to a subpopulation of 65 year olds with the same disease stage (e.g., stage 2):

\[
\log\{\lambda(t \mid \text{age} = 66, \text{stage} = 2)\} - \log\{\lambda(t \mid \text{age} = 65, \text{stage} = 2)\} = \beta_1
\]

- $\beta_1$ is the log-relative hazard (hazard ratio) comparing two subjects that differ in age at diagnosis by one year and have the same stage of disease

- $e^{\beta_1}$ is the hazard ratio comparing two populations that differ in age at diagnosis by one year and have the same stage of disease
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Laryngeal Cancer Example - Multiple Regression

▶ What is the interpretation of \( e^{\beta_3} \)?

Notes

▶ it does not matter what age the two subpopulations are (just that they be the same) – the effect of stage is (assumed to be) the same

▶ the model assumes the effect of stage of disease is the same, regardless of the subject’s age

▶ and, that the effect of age is the same, regardless of the subject’s stage of disease
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Estimation in R

- Again, use `coxph()` to fit the model
- Use `factor()` to create dummy variables for `stage`

```r
> fit <- coxph(Surv(t2death, death) ~ age + factor(stage), data=larynx)
> summary(fit)

          coef exp(coef) se(coef)  z  Pr(>|z|)    
age     0.0190  1.0192  0.0143  1.33  0.182
factor(stage)2 0.1400  1.1503  0.4625  0.30  0.762
factor(stage)3 0.6424  1.9010  0.3561  1.80  0.071 .
factor(stage)4 1.7060  5.5068  0.4219  4.04  5.3e-05 ***

---

Signif. codes:  0 ** ** ** 0.001 ** 0.01 * 0.05 . 0.1 1

exp(coef) exp(-coef) lower .95 upper .95
age             1.02     0.981   0.991   1.05
factor(stage)2  1.15     0.869   0.465   2.85
factor(stage)3  1.90     0.526   0.946   3.82
factor(stage)4  5.51     0.182   2.409  12.59

Rsquare= 0.184  (max possible= 0.987 )
Likelihood ratio test= 18.3  on 4 df,  p=0.00107
Wald test = 21.1  on 4 df,  p=0.000296
Score (logrank) test = 24.8  on 4 df,  p=5.57e-05
```
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Model interpretations

▶ We estimate that the risk of death among stage 3 subjects is 1.90 times higher than that of stage 1 patients that are similar with respect to age at diagnosis.

▶ Among populations of patients that are similar with respect to stage, we estimate that a 2% greater risk of death is associated with a 1-year increase in age at diagnosis.

▶ Suppose we were interested in the 5-year effect of age. Then $5 \times \beta_1$ is the log-relative hazard comparing populations that differ in age at diagnosis by five years:

▶ Could re-fit the model, using $I(age/5)$, or the `linContr.coxph()` function on the course webpage.

```r
> linContr.coxph( model=fit, contr.names="age", contr.coef=5 )
```

Test of $H_0: \exp(5*age) = 1$:

```
   exp( Est ) se.est zStat  pVal ci95.lo ci95.hi
 1    1.1   0.071 1.335 0.182   0.956  1.265
```
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Model interpretations

▶ Suppose we wished to compare the age-adjusted hazard for stage 3 subjects to that of a stage 2 subjects . . .

**Example:** compare stage 3 65 year-olds to a stage 2 65-year olds:

\[
\log \{ \lambda(t \mid \text{age} = 65, \text{stage} = 3) \} - \log \{ \lambda(t \mid \text{age} = 65, \text{stage} = 2) \}
\]

▶ \((\beta_3 - \beta_2)\) is the log-hazard ratio of stage 3 subjects compared to stage 2 subjects who are similar in age.
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Model interpretations

- Note that inference will require $\widehat{\text{Cov}}[\widehat{\beta}_2, \widehat{\beta}_3]$

- Again, we can use `linConstr.coxph()` for the estimation...

```r
> linConstr.coxph( model=fit,
  contr.names=c("factor(stage)3", "factor(stage)2"),
  contr.coef=c(1,-1) )
```

Test of $H_0: \exp(1 \times \text{factor(stage)3} + -1 \times \text{factor(stage)2}) = 1$

```
exp( Est  )  se.est  zStat  pVal  ci95.lo  ci95.hi
1    1.653   0.452  1.112  0.266   0.682   4.005
```
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Model interpretations

▶ What about a global (overall, construct) test of the effect of stage? That is, we wish to test:

\[ H_0 : \]
\[ H_A : \]

▶ One possibility is to conduct a likelihood ratio test using the `anova()` function

```r
> fit.red <- coxph( Surv( t2death, death ) ~ age, data=larynx )
> anova(fit.red, fit)

Analysis of Deviance Table
  Cox model: response is Surv(t2death, death)
  Model 1: ~ age
  Model 2: ~ age + factor(stage)
    loglik Chisq Df P(>|Chi|)
1  -196
2  -188  15.7 3  0.0013 **
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1  1
```
### Investigate Effect Modification

**Q:** Does stage of disease have a different effect for different ages?

**Consider the model with interaction terms:**

\[
\lambda(t) = \lambda_0(t) \exp\{\beta_1 \text{aged} x_i + \beta_2 \mathbb{1}(\text{stage} = 2) \\
+ \beta_3 \mathbb{1}(\text{stage} = 3) + \beta_4 \mathbb{1}(\text{stage} = 4) \\
+ \beta_5 \text{aged} x_i \times \mathbb{1}(\text{stage} = 2) \\
+ \beta_6 \text{aged} x_i \times \mathbb{1}(\text{stage} = 3) \\
+ \beta_7 \text{aged} x_i \times \mathbb{1}(\text{stage} = 4)\}
\]
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Investigate Effect Modification

> fit.int <- coxph(Surv(t2death, death) ~ age*factor(stage), data=larynx)
> summary(fit.int)

|        | coef     | exp(coef) | se(coef) | z     | Pr(>|z|) |
|--------|----------|-----------|----------|-------|----------|
| age    | -0.002932| 0.997073  | 0.026084 | -0.11 | 0.911    |
| factor(stage)2 | -8.083763| 0.000309  | 3.693631 | -2.19 | 0.029 *  |
| factor(stage)3 | -0.164044| 0.848705  | 2.474158 | -0.07 | 0.947    |
| factor(stage)4 | 0.825262 | 2.282480  | 2.422927 | 0.34  | 0.733    |
| age:factor(stage)2 | 0.122363| 1.130165  | 0.052528 | 2.33  | 0.020 *  |
| age:factor(stage)3 | 0.012034| 1.012106  | 0.037539 | 0.32  | 0.749    |
| age:factor(stage)4 | 0.014224| 1.014325  | 0.035931 | 0.40  | 0.692    |

<table>
<thead>
<tr>
<th></th>
<th>exp(coef)</th>
<th>exp(-coef)</th>
<th>lower .95</th>
<th>upper .95</th>
</tr>
</thead>
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<td>age</td>
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<td>factor(stage)2</td>
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<td>1.014325</td>
<td>0.986</td>
<td>9.45e-01</td>
<td>1.09</td>
</tr>
</tbody>
</table>

Rsquare= 0.24     (max possible= 0.987 )
Likelihood ratio test= 24.7 on 7 df,  p=0.00087
Wald test        = 24.5 on 7 df,  p=0.000932
Score (logrank) test = 29.1 on 7 df,  p=0.000137
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Investigate Effect Modification

- Note: $\beta_5$ appears significantly different from 0, but is this by itself meaningful?...Beware of spurious subgroup effects!

- Global LRT for whether the interaction terms are significant

\[
H_0 : \beta_5 = \beta_6 = \beta_7 = 0 \\
H_A : \beta_5 \neq 0 \text{ or } \ldots \text{ or } \beta_7 \neq 0
\]

> anova(fit, fit.int)
Analysis of Deviance Table
  Cox model: response is Surv(t2death, death)
  Model 1: ~ age + factor(stage)
  Model 2: ~ age * factor(stage)
          loglik Chisq Df P(>|Chi|)
1          -188          
2          -184  6.35 3  0.096 .
---
Signif. codes:  0 Ô***Ô 0.01 Ô**Ô 0.001 Ô*Ô 0.05 Ô.O 0.1 Ô O 1
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Investigate Effect Modification

- We do not reject the hypothesis that age and stage of disease interact in their association with mortality due to laryngeal cancer
  - Globally, age does not modify the effect of stage of disease
  - Globally, stage of disease does not modify the effect of age
  - Not very strong evidence to suggest that one factor modifies the effect of the other
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Investigate Effect Modification

- Parameter interpretation: $\beta_5$ through $\beta_7$:
  - Compare stage 3 70 year olds to a stage 1 70 year olds

\[
\log\{\lambda_2(t \mid \text{age} = 70, \text{stage} = 3)\} - \log\{\lambda_1(t \mid \text{age} = 70, \text{stage} = 1)\}
\]

$\Rightarrow (\beta_3 + 70\beta_6)$ is the log-relative hazard comparing these two subpopulations
Investigate Effect Modification

▶ From the output below, we estimate that the risk of death among 70 year old stage 3 patients is approximately 1.97-times that of 70 year old stage 1 patients (95% CI: 0.904, 4.298). This result is not significant based upon a level .05 test.

```r
> linContr.coxph( model=fit.int,
    contr.names=c("factor(stage)3", "age:factor(stage)3"),
    contr.coef=c(1,70) )

Test of H_0: exp( 1*factor(stage)3 + 70*age:factor(stage)3 ) = 1 :

    exp( Est ) se.est  zStat  pVal  ci95.lo  ci95.hi
1 1.971 0.398 1.705 0.088 0.904 4.298
```
Cox Model Summary

Summary

- $\beta_k$ is the difference in the log-hazard function comparing two subpopulations differing in $x_k$ by 1-unit that are similar with respect to all other covariates in the model.

- In the absence of interaction terms, the contrast expressed by $\beta_k$ is adjusted for all other covariate in the model, so it has the interpretation of a log-relative hazard associated with a change in $x_k$, holding other covariates constant at some fixed value.

- Interaction terms are log-ratios of relative risks.

- To interpret interaction terms, remember that if you have the interaction of $x_1$ and $x_2$ in the model, to describe the effect of $x_1$, you must fix $x_2$ at a particular value.
Cox Model Summary

Summary

- You can *always* check your interpretation by comparing two imaginary populations with different covariate values (as we have done here) and see how their log-relative hazard is expressed in terms of the $\beta_k$s.

- For continuous covariates, it can be useful to *center them* before multiplying to obtain interaction terms.

- The proportional hazards model is indeed a model for the *hazard* more than a model for *survival time*, although they are related.

Why? Because it focuses on the risk sets.