PLSC 504 - Fall 2017
Cox's Proportional Hazards Model

September 26, 2017

Cox (1972)

Basic idea:

$$h_i(t) = h_0(t)\exp(\mathbf{X}_i\beta)$$

Note:

- $h_0(t) \equiv h(t|\mathbf{X} = 0)$
- Changes in $\mathbf{X}$ shift $h(t)$ *proportionally*

Cox (1972) (continued)

$$\begin{aligned} \text{HR} &= \frac{h_0(t)\exp(X_1\hat{\beta})}{h_0(t)\exp(X_0\hat{\beta})} \\ &= \exp[(1-0)\hat{\beta}] \\ &= \exp(\hat{\beta}) \end{aligned}$$

Cox (1972) (continued)

Also, because

$$S(t) = \exp[-H(t)]$$

then

$$\begin{aligned} S(t) &= \exp\left[-\int_0^t h(t)\,dt\right] \\ &= \exp\left[-\exp(\mathbf{X}_i\beta)\int_0^t h_0(t)\,dt\right] \\ &= \left[\exp\left(-\int_0^t h_0(t)\,dt\right)\right]^{\exp(\mathbf{X}_i\beta)} \\ &= [S_0(t)]^{\exp(\mathbf{X}_i\beta)} \end{aligned}$$

Partial Likelihood

Assume N_C distinct event times t_j, with no "ties."

Then:

$$\begin{aligned}
&\Pr(\text{Individual } k \text{ experienced the event at } t_j \mid \textit{One} \text{ observation experienced the event at } t_j) \\
&\qquad = \frac{\Pr(\text{At-risk observation } k \text{ experiences the event of interest at } t_j)}{\Pr(\text{One at-risk observation experiences the event of interest at } t_j)} \\
&\qquad = \frac{h_k(t_j)}{\sum_{\ell \in R_j} h_\ell(t_j)}
\end{aligned}$$

Partial Likelihood (continued)

$$\begin{aligned} L_i &= \frac{h_0(t_j)\exp(\mathbf{X}_i\beta)}{\sum_{\ell \in R_j} h_0(t_j)\exp(\mathbf{X}_\ell\beta)} \\ &= \frac{h_0(t_j)\exp(\mathbf{X}_i\beta)}{h_0(t_j)\sum_{\ell \in R_j} \exp(\mathbf{X}_\ell\beta)} \\ &= \frac{\exp(\mathbf{X}_i\beta)}{\sum_{\ell \in R_j} \exp(\mathbf{X}_\ell\beta)} \end{aligned}$$

$$L = \prod_{i=1}^{N} \left[\frac{\exp(\mathbf{X}_i\beta)}{\sum_{\ell \in R_j} \exp(\mathbf{X}_\ell\beta)} \right]^{C_i}$$

$$\ln L = \sum_{i=1}^{N} C_i \left\{ \mathbf{X}_i\beta - \ln \left[\sum_{\ell \in R_j} \exp(\mathbf{X}_\ell\beta) \right] \right\}$$

Notes on Partial Likelihood

- PL is
  - Consistent
  - Asymptotically normal
  - Slightly inefficient (but asymptotically efficient)
- Considers <u>order</u> of events, but not actual <u>duration</u>
- Censored events: Modify R_j
- No <u>ties</u>

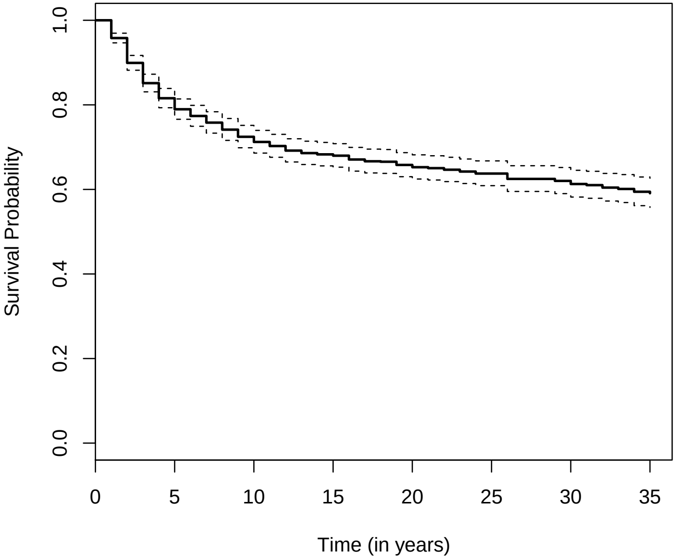
Example: Interstate War, 1950-1985

- Dyad-years for "politically-relevant" dyads
- $N = 827$, $NT = 20448$.
- Covariates:
  - Whether (=1) or not the two countries are *allies*,
  - Whether (=1) or not the two countries are *contiguous*,
  - The *capability ratio* of the two countries,
  - The lower of the two countries' (GDP) *growth* (rescaled),
  - The lower of the two countries' *democracy* (POLITY IV) scores (rescaled to [-1,1]), and
  - The amount of *trade* between the two countries, as a fraction of joint GDP.

The Data

```
> summary(OR)
     dyadid            year          start            stop           futime
 Min.   :  2020   Min.   :1951   Min.   : 0.00   Min.   : 1.00   Min.   : 5.00
 1st Qu.:100365   1st Qu.:1965   1st Qu.: 5.00   1st Qu.: 6.00   1st Qu.:23.00
 Median :220235   Median :1972   Median :11.00   Median :12.00   Median :31.00
 Mean   :253305   Mean   :1971   Mean   :12.32   Mean   :13.32   Mean   :28.97
 3rd Qu.:365600   3rd Qu.:1979   3rd Qu.:19.00   3rd Qu.:20.00   3rd Qu.:35.00
 Max.   :900920   Max.   :1985   Max.   :34.00   Max.   :35.00   Max.   :35.00
    dispute            allies           contig           trade
 Min.   :0.00000   Min.   :0.0000   Min.   :0.0000   Min.   :0.00000
 1st Qu.:0.00000   1st Qu.:0.0000   1st Qu.:0.0000   1st Qu.:0.00000
 Median :0.00000   Median :0.0000   Median :0.0000   Median :0.00020
 Mean   :0.01981   Mean   :0.3563   Mean   :0.3099   Mean   :0.00231
 3rd Qu.:0.00000   3rd Qu.:1.0000   3rd Qu.:1.0000   3rd Qu.:0.00120
 Max.   :1.00000   Max.   :1.0000   Max.   :1.0000   Max.   :0.17680
     growth             democracy          capratio
 Min.   :-0.264900   Min.   :-1.0000   Min.   : 0.0100
 1st Qu.:-0.004800   1st Qu.:-0.8000   1st Qu.: 0.0462
 Median : 0.014700   Median :-0.7000   Median : 0.2220
 Mean   : 0.007823   Mean   :-0.3438   Mean   : 1.6677
 3rd Qu.: 0.027800   3rd Qu.: 0.2000   3rd Qu.: 1.1560
 Max.   : 0.164700   Max.   : 1.0000   Max.   :78.9296
```

The Data (Kaplan-Meier plot)



Software

R:

- `coxph` in `survival` (preferred)
- `cph` in `design`
- Plots: `plot(survfit(PHobject))`

Stata:

- Basic command = `stcox`
- `stset` first
- Options: `robust`, various methods for ties, postestimation commands

Model Fitting

```
> ORCox.br<-coxph(OR.S~allies+contig+capratio+growth+democracy+trade,
                data=OR,na.action=na.exclude,method="breslow")

> summary(ORCox.br)

  n= 20448, number of events= 405

              coef exp(coef) se(coef)      z Pr(>|z|)
allies    -0.34849   0.70576  0.11096 -3.141 0.001686 **
contig     0.94861   2.58213  0.12173  7.793 6.55e-15 ***
capratio  -0.22303   0.80009  0.05164 -4.319 1.57e-05 ***
growth    -3.69487   0.02485  1.19950 -3.080 0.002068 **
democracy -0.38194   0.68254  0.09915 -3.852 0.000117 ***
trade     -3.22857   0.03961  9.45588 -0.341 0.732776
---
Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1
.
.
.
```

Model Fitting (continued)

```
.
.
.
          exp(coef) exp(-coef) lower .95 upper .95
allies      0.70576     1.4169 5.678e-01 8.772e-01
contig      2.58213     0.3873 2.034e+00 3.278e+00
capratio    0.80009     1.2499 7.231e-01 8.853e-01
growth      0.02485    40.2402 2.368e-03 2.608e-01
democracy   0.68254     1.4651 5.620e-01 8.289e-01
trade       0.03961    25.2436 3.540e-10 4.433e+06

Concordance= 0.714  (se = 0.015 )
Rsquare= 0.01   (max possible= 0.234 )
Likelihood ratio test= 210.3  on 6 df,   p=0
Wald test            = 159.8  on 6 df,   p=0
Score (logrank) test = 185.8  on 6 df,   p=0
```

Interpretation: Hazard Ratios

$$HR = \exp[(\mathbf{X}_j - \mathbf{X}_k)\hat{\beta}]$$

Means:

- $HR = 1 \;\leftrightarrow\; \hat{\beta} = 0$
- $HR > 1 \;\leftrightarrow\; \hat{\beta} > 0$
- $HR < 1 \;\leftrightarrow\; \hat{\beta} < 0$

Percentage difference $= 100 \times \{\exp[(\mathbf{X}_j - \mathbf{X}_k)\hat{\beta}] - 1\}$.

Example: Hazard Ratios

From above:

```
          exp(coef) exp(-coef) lower .95 upper .95
allies      0.70576     1.4169 5.678e-01 8.772e-01
contig      2.58213     0.3873 2.034e+00 3.278e+00
capratio    0.80009     1.2499 7.231e-01 8.853e-01
growth      0.02485    40.2402 2.368e-03 2.608e-01
democracy   0.68254     1.4651 5.620e-01 8.289e-01
trade       0.03961    25.2436 3.540e-10 4.433e+06
```

Interpretation:

- Countries which are *allies* have an expected $(0.706 - 1) \times 100) = 29.4$ percent lower hazard of conflict than those that are not.
- *Contiguous* countries have $(2.582 - 1) \times 100 = 158$ percent higher hazards of conflict than non-contiguous ones.
- A one-unit increase in *democracy* corresponds to a $(0.683 - 1) \times 100 = 31.7$ percent decrease in the expected hazard of conflict.

Hazard Ratios: Scaling Covariates

It is good for one-unit changes to be meaningful / realistic...

```
> OR$growthPct<-OR$growth*100
> summary(coxph(OR.S~allies+contig+capratio+growthPct+democracy+trade,
               data=OR,na.action=na.exclude, method="breslow"))
.
.
.
          exp(coef) exp(-coef) lower .95 upper .95
allies      0.70576     1.4169 5.678e-01 8.772e-01
contig      2.58213     0.3873 2.034e+00 3.278e+00
capratio    0.80009     1.2499 7.231e-01 8.853e-01
growthPct   0.96373     1.0376 9.413e-01 9.867e-01
democracy   0.68254     1.4651 5.620e-01 8.289e-01
trade       0.03961    25.2436 3.540e-10 4.433e+06
```

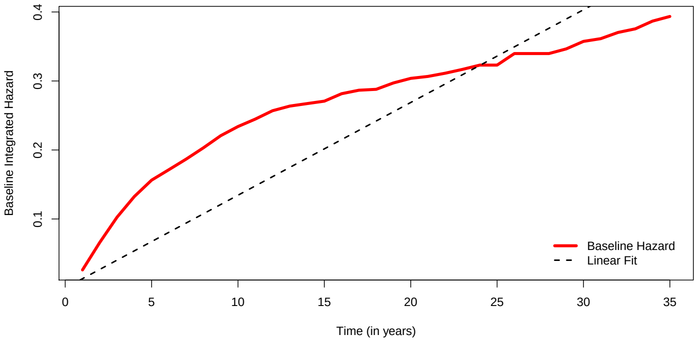
Note:

- Previous HR for `growth` $= 0.02485 \rightarrow 97.5$ percent decrease in $\hat{h}(t)$
- HR for `growthPct` is now 0.964; 1 unit increase $\rightarrow$ 4% decrease in $\hat{h}(t)$
- Same result, proportionally: $0.96373^{100} = 0.02485$

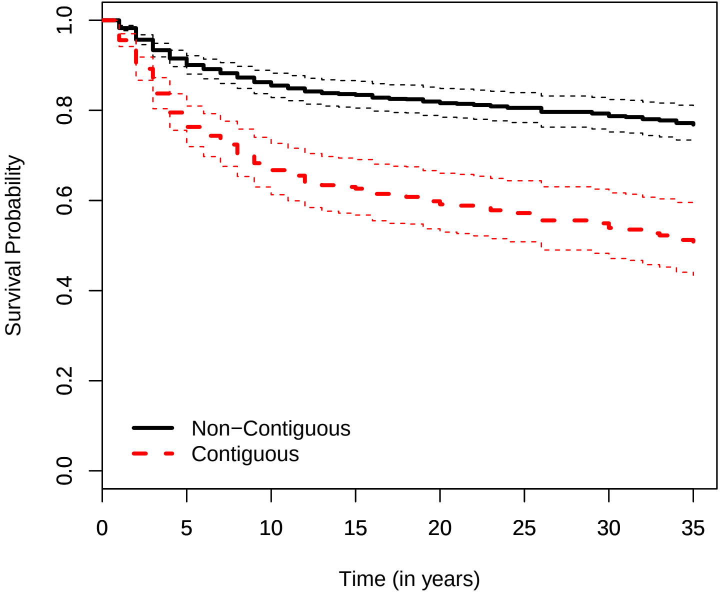
Baseline Hazards

Because the Cox model is semiparametric, it uses a conventional / univariate (Nelson-Aalen) estimate of the "baseline" hazard:

```
OR.BH<-basehaz(ORCox.br,centered=FALSE)
```



Comparing Survival Curves



Ties...

$\exists$ ties...

Their presence biases Cox $\hat{\beta}$s toward zero.

- Call $d_j > 0$ the number of events occurring at t_j, and
- D_j the set of d_j observations that have the event at t_j.

Ties (continued)

Means of handling ties:

- Breslow:

$$L_{\text{Breslow}}(\beta) = \prod_{i=1}^{N} \frac{\exp\left[\left(\sum_{q \in D_j} \mathbf{X}_q\right)\beta\right]}{\left[\sum_{\ell \in R_j} \exp(\mathbf{X}_\ell \beta)\right]^{d_j}}$$

- Efron

$$\ln L_{\text{Efron}}(\beta) = \sum_{j=1}^{J} \sum_{i \in D_j} \left\{ \mathbf{X}_i \beta - \frac{1}{d_j} \sum_{k=1}^{d_j - 1} \ln \left[\sum_{\ell \in R_j} \exp(\mathbf{X}_\ell \beta) - k \left(\frac{1}{d_j} \sum_{\ell \in D_j} \exp(\mathbf{X}_\ell \beta) \right) \right] \right\}$$

Ties (continued)

- "Exact" (partial likelihood)

$$\ln L_{\text{Exact}}(\boldsymbol{\beta}) = \sum_{j=1}^{J} \left\{ \sum_{i \in R_j} \delta_{ij}(\mathbf{X}_i \boldsymbol{\beta}) - \ln[f(r_j, d_j)] \right\}$$

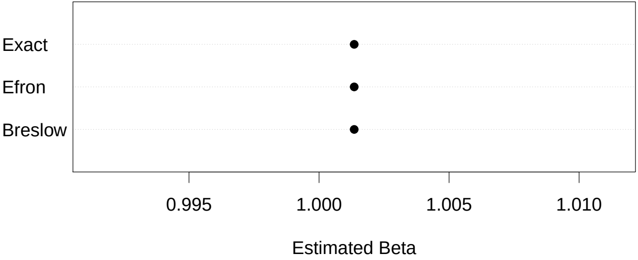
where

$$\begin{aligned} f(r,d) &= g(r-1,d) + g(r-1,d-1)\exp(\mathbf{X}_k \boldsymbol{\beta}), \\ k &= r\text{th observation in } R_j, \\ r_j &= \text{cardinality of } R_j, \text{ and} \\ g(r,d) &= \begin{cases} 0 \text{ if } r < d, \\ 1 \text{ if } d = 0 \end{cases} \end{aligned}$$

Ties: Example

```
set.seed(7222009)
Data<-as.data.frame(cbind(c(rep(1,times=400)),
            c(rep(c(0,1),times=200))))
colnames(Data)<-c("C","X")
Data$T<-rexp(400,exp(0+1*Data$X)) # B = 1.0
Data.S<-Surv(Data$T,Data$C)

D.br<-coxph(Data.S~X,data=Data,method="breslow")
D.ef<-coxph(Data.S~X,data=Data,method="efron")
D.ex<-coxph(Data.S~X,data=Data,method="exact")
```

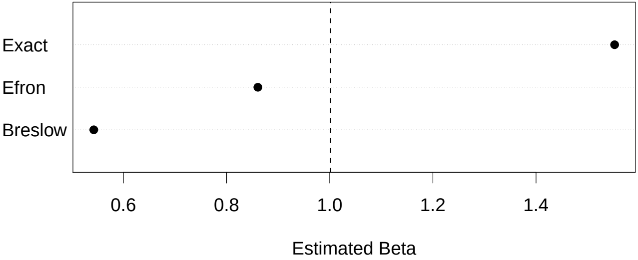


Ties: Example (continued)

```
Data$Tied<-round(Data$T,0)

DataT.S<-Surv(Data$Tied,Data$C)

DT.br<-coxph(DataT.S~X,data=Data,method="breslow")
DT.ef<-coxph(DataT.S~X,data=Data,method="efron")
DT.ex<-coxph(DataT.S~X,data=Data,method="exact")
```



Ties: Practical Advice

- All approx. are identical if $\nexists$ ties
- Few ties $=$ similar results
- When ties are present, Breslow $<$ Efron $<$ "Exact" methods
- If you want to learn more about ties in the Cox model, read this.

Cox vs. Parametric Models

Conceptual considerations:

- Theory
- Nature of $h(t)$
- Relative importance: Bias vs. efficiency
- Need / willingness for out-of-sample predictions / forecasting

Cox, On His Model

Reid: "What do you think of the cottage industry that's grown up around [the Cox model]?"

Cox: "In the light of further results one knows since, I think I would normally want to tackle the problem parametrically... I'm not keen on non-parametric formulations normally."

Reid: "So if you had a set of censored survival data today, you might rather fit a parametric model, even though there was a feeling among the medical statisticians that that wasn't quite right."

Cox: "That's right, but since then various people have shown that the answers are very insensitive to the parametric formulation of the underlying distribution. And if you want to do things like predict the outcome for a particular patient, it's much more convenient to do that parametrically."

– From Reid (1994).

Extensions (future classes)

- Cox Models for *repeated events*
- Models with "frailties"
- Competing risks / "cured" subpopulations
- etc.