Survival Analysis part 2

Adam J Sullivan, PhD

03/21/2018

Cox-PH Regression

Physicians Health Study and Aspirin

Recall the Colorectal Cancer component of the Physicians Health Study

NAME	DESCRIPTION
age	Age in years at time of Randomization
asa	0 - placebo, 1 - aspirin
bmi	Body Mass Index (kg/m^2)
hypert	1 - Hypertensive at baseline, 0 - Not
alcohol	0 - less than monthly, 1 - monthly to less than daily, 2 - daily consumption

NAME	DESCRIPTION
dm	0 = No diabetes Mellitus, 1 - diabetes Mellitus
sbp	Systolic BP (mmHg)
exer	0 - No regular, 1 - Sweat at least once per week
csmoke	0 - Not currently, 1 - < 1 pack per day, 2 - $\geq$ 1 pack per day
psmoke	0 - never smoked, 1 - former < 1 pack per day, 2 - former $\geq$ 1 pack per day
pkyrs	Total lifetime packs of cigarettes smoked
crc	0 - No colorectal Cancer, 1 - Colorectal cancer
cayrs	Years to colorectal cancer, or death, or end of follow-up.

For this study each participant contributed 2 pieces of information during follow-up:

1. Information on whether of not they had a Colorectal Cancer(CRC) during follow-up
2. Follow-up time in years, specified as time from randomization until first of
   - end of Study
   - death
   - Colorectal Cancer
   - Loss to follow-up

We can load this data into R.

```
library(tidyverse)
library(haven)
phscrc <- read_dta("phscrc.dta")
phscrc <- phscrc %>% mutate(age.cat = cut(age, c(40, 50, 60,
    70, 90), right = FALSE)) %>% mutate(alcohol.use = factor(alcohol >
    1, labels = c("no", "yes"))) %>% mutate(obese = factor(bmi >
    30, labels = c("Not Obese", "Obese")))
```

Proportional Hazards Model

The general ***Proportional Hazards Model*** is

$$h(t|X_1, \ldots, X_p) = h_0(t) \exp(\beta_1 x_1 + \cdots + \beta_p x_p)$$

$$\text{or}$$

$$\log[h(t|X_1, \ldots, X_p)] = \log[h_0(t)] + \beta_1 x_1 + \cdots + \beta_p x_p$$

where $h_0(t)$ is the baseline hazard function and the "intercept" is $\log[h_0(t)]$.

Semi-Parametric Regression

- Weibull and Exponential are examples of parametric proportional hazards models, where $h_0(t)$ is a specified function.
- In 1972, Cox generalized these types of models so that we can make inferences on the $\beta_1, \ldots, \beta_p$ without specifying $h_0(t)$.
- We call Cox a semi-parametric regression model
- We fit this using something called *Partial Likelihood Estimation*
- Once again we use an algorithm to maximize the partial likelihood.

Interpeting the Model

Let

- $X = 0$ be the control group
- $X = 1$ be the treatment group

Then

$$\begin{aligned} h(t|X=x) &= h_0(t)\exp(\beta x) \\ h(t|X=0) &= h_0(t) \\ &= \text{ baseline hazard for control group} \\ h(t|X=1) &= h_0(t)\exp(\beta) \\ &= \text{ hazard for treated group} \\ \exp(\beta) &= \frac{h(t|X=1)}{h(t|X=0)} \end{aligned}$$

What Does This Mean?

- This means that the hazard ratio is constant over time (**Proportional Hazards**)
- β is the log hazard ratio or log-relative risk
- According to the Cox model

$$
\begin{aligned}
\log[h]h(t|X=0)] &= \log[h_0(t)] \\
\log[h]h(t|X=1)] &= \log[h_0(t)] + \beta
\end{aligned}
$$

- This means the log of the hazard functions are parallel over time.
- We make no assumptions about $h_0(t)$.

Verifying Proportional Hazards Assumption

Recall

$$S(t) = \exp(-\Lambda(t))$$

with a binary X we have that

$$\begin{aligned}
\Lambda_1(t) &= \Lambda_0(t)\exp(\beta) \\
S_0(t) &= \exp(\Lambda_0(t)) \\
-\log(S_0(t)) &= \Lambda_0(t) \\
\log(-\log(S_0(t))) &= \log(\Lambda_0(t))
\end{aligned}$$

$$\begin{aligned}
S_1(t) = exp(-\Lambda_1(t)) &= \exp[\Lambda_0(t)\exp(\beta)] \\
-\log(S_1(t)) &= \Lambda_0(t)\exp(\beta) \\
\log(-\log(S_1(t))) &= \log(\Lambda_0(t)) + \beta
\end{aligned}$$

Verifying Proportional Hazards Assumption

- Thus we can see that under the assumption of ***proportional hazards***
  - $\log(-\log(K-M))$ should be parallel over time.
  - We typically verify this graphically.
  - Recall the CRC study:

Example: Kaplan-Meier Survival

```
library(survival)

model <- survfit(Surv(cayrs, crc) ~ alcohol.use, data = subset(phscrc,
    cayrs > 0))
model
```

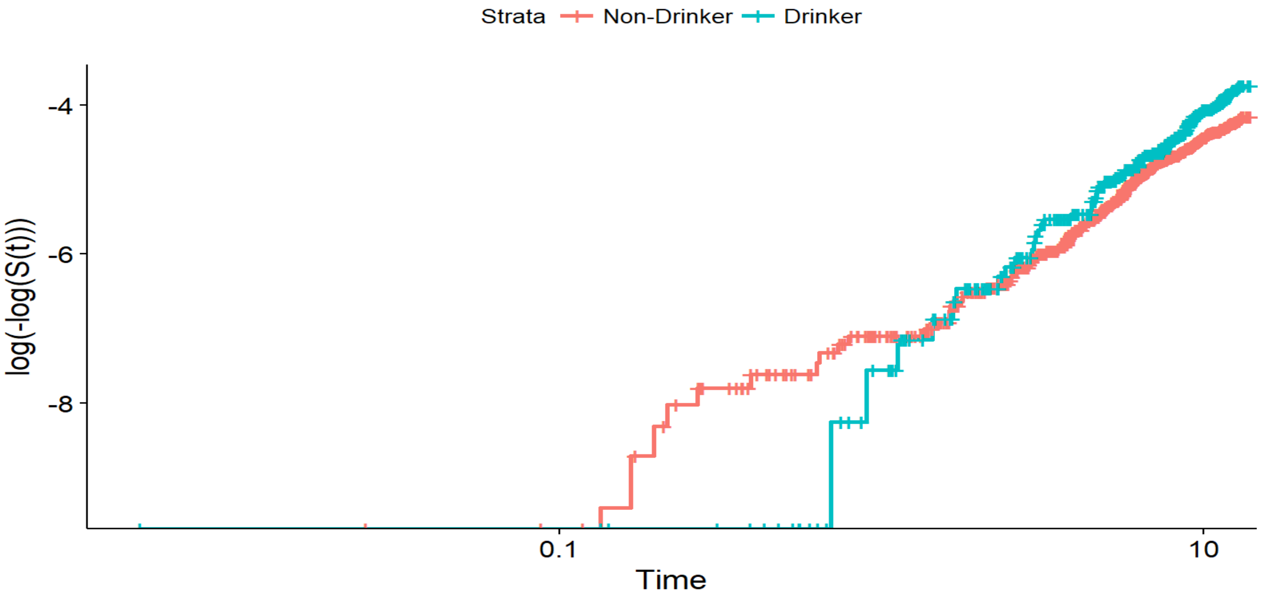
Example: Kaplan-Meier Survival

```
## Call: survfit(formula = Surv(cayrs, crc) ~ alcohol.use, data = subset(phscrc,
##     cayrs > 0))
##
##                     n events median 0.95LCL 0.95UCL
## alcohol.use=no  12162    173     NA      NA      NA
## alcohol.use=yes  3856     81     NA      NA      NA
```

Plotting the Kaplan-Meier

```
library(survminer)
ggsurvplot(model, legend.labs = c("Non-Drinker", "Drinker"),
    break.time.by = 2, fun = "cloglog")
```

Plotting the Kaplan-Meier



Cox PH in R

- We can run the Cox PH in R:

```
cox.crc <- coxph(Surv(cayrs, crc) ~ alcohol.use, data = subset(phscrc,
    cayrs > 0))
summary(cox.crc)
```

Cox PH in R

```
## Call:
## coxph(formula = Surv(cayrs, crc) ~ alcohol.use, data = subset(phscrc, 
##     cayrs > 0))
## 
##   n= 16018, number of events= 254 
## 
##                  coef exp(coef) se(coef)    z Pr(>|z|)   
## alcohol.useyes 0.414     1.514    0.135 3.08   0.0021 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
## 
##                exp(coef) exp(-coef) lower .95 upper .95
## alcohol.useyes      1.51      0.661      1.16      1.97
## 
## Concordance= 0.541  (se = 0.013 )
## Rsquare= 0.001   (max possible= 0.262 )
## Likelihood ratio test= 8.97  on 1 df,   p=0.00275
## Wald test            = 9.48  on 1 df,   p=0.00208
## Score (logrank) test = 9.61  on 1 df,   p=0.00193
```

Interpretation

- This would suggest that the hazard of Colorectal Cancer for those who drink daily is 51% higher than those who drink less than daily.

Continuous Example of Cox PH

- Let's consider `age` and `smoking`:

```
library(survival)
crc.cox <- coxph(Surv(cayrs, crc) ~ csmok + age, data = subset(phscrc,
    cayrs > 0))
summary(crc.cox)
```

Continuous Example of Cox PH

```
## Call:
## coxph(formula = Surv(cayrs, crc) ~ csmok + age, data = subset(phscrc,
##     cayrs > 0))
##
##   n= 16018, number of events= 254
##
##          coef exp(coef) se(coef)     z Pr(>|z|)
## csmok 0.31715   1.37320  0.09767  3.25   0.0012 **
## age   0.07904   1.08224  0.00628 12.58   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##       exp(coef) exp(-coef) lower .95 upper .95
## csmok      1.37      0.728      1.13      1.66
## age        1.08      0.924      1.07      1.10
##
## Concordance= 0.724  (se = 0.018 )
## Rsquare= 0.01   (max possible= 0.262 )
## Likelihood ratio test= 160  on 2 df,   p=0
## Wald test            = 163  on 2 df,   p=0
## Score (logrank) test = 177  on 2 df,   p=0
```

Interpretation

- Then we could say that for two people with the same smoking status a one year increase in age would lead to an 8.2% increase in the hazard of colorectal cancer with a 95% CI of 6.9% to 9.6%.
- We would also be able to say that for 2 people the same age, a person who is a current smoker would have a 37% increase in hazard of colorectal cancer than a non smoker.

Cox-PH Regression

Assessing Diagnostics and Model Fit with Cox-PH

- With the Cox PH model we will consider 2 things
  - Checking Proportional Hazards Assumption
  - Checking for Influential Observations

The Data

- We will consider Recidivism of 432 male patients.
- They all were observed for 1 year prior to release from prison.
- The following slides will contain the variables.

Variables

VARIABLE	DESCRIPTION
week	week of first arrest after release, or censoring time.
arrest	the event indicator, equal to 1 for those arrested during the period of the study and 0 for those who were not arrested.
fin	a factor, with levels yes if the individual received financial aid after release from prison, and no if he did not; financial aid was a randomly assigned factor manipulated by the researchers.

Variables

VARIABLE	DESCRIPTION
age	in years at the time of release.
wexp	a factor with levels yes if the individual had full-time work experience prior to incarceration and no if he did not.
mar	a factor with levels married if the individual was married at the time of release and not married if he was not.
paro	a factor coded yes if the individual was released on parole and no if he was not.
prior	number of prior convictions.

Variables

VARIABLE	DESCRIPTION
educ	education, a categorical variable coded numerically, with codes 2 (grade 6 or less), 3 (grades 6 through 9), 4 (grades 10 and 11), 5 (grade 12), or 6 (some post-secondary).6
emp1 – emp52	factors coded yes if the individual was employed in the corresponding week of the study and no otherwise.
race	a factor with levels black and other.

Reading Data in

```
url <- "http://socserv.mcmaster.ca/jfox/Books/Companion/data/Rossi.txt"
Rossi <- read.table(url, header = TRUE)
```

Our Model

```r
library(survival)
library(tidyverse)
library(broom)
mod1 <- coxph(Surv(week, arrest) ~ fin + age + race + wexp +
    mar + paro + prio, data = Rossi)
tidy1 <- tidy(mod1, exponentiate = T)
knitr::kable(tidy1[-c(3, 4)])
```

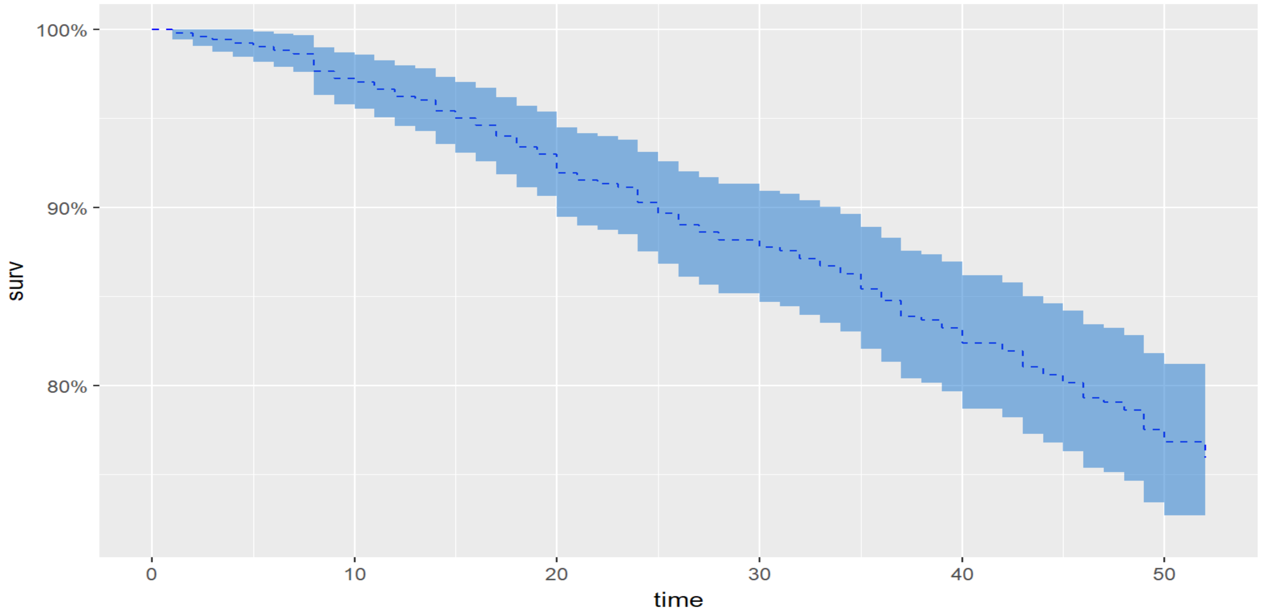
Our Model

TERM	ESTIMATE	P.VALUE	CONF.LOW	CONF.HIGH
finyes	0.684	0.047	0.470	0.996
age	0.944	0.009	0.904	0.986
raceother	0.731	0.308	0.399	1.336
wexpyes	0.861	0.480	0.568	1.305
marnot married	1.543	0.256	0.730	3.261
paroyes	0.919	0.665	0.626	1.348
prio	1.096	0.001	1.036	1.159

Plotting Regression

```
library(ggplot2)
library(ggfortify)
autoplot(survfit(mod1), surv.linetype = "dashed", surv.colour = "blue",
    conf.int.fill = "dodgerblue3", conf.int.alpha = 0.5, censor = FALSE)
```

Plotting Regression



Checking Proportional Hazards

- We have tested these before with Schoenfeld Residuals
- We can do this with the `cox.zph()` function.

Checking Proportional Hazards

```
cox.zph(mod1)
```

```
##                     rho    chisq        p
## finyes          0.00646  0.00502 0.943519
## age            -0.26455 11.27897 0.000784
## raceother       0.11224  1.41652 0.233977
## wexpyes         0.22976  7.14021 0.007537
## marnot married -0.07295  0.68627 0.407435
## paroyes        -0.03618  0.15496 0.693841
## prio           -0.01366  0.02304 0.879353
## GLOBAL               NA 17.65862 0.013609
```

Conclusion

- We see there is an issue
    - `age` is an issue
    - `wexp` is an issue as well.
- What do we do???

Enter Stratification

- We can adjust for a variable that does not meet the proportional hazards assumption by stratification.
- Assume we have Z which does not allow for PH

$$h(t|X, Z = j) = h_j(t) exp(X\beta)$$

- $j = 1, ldots, C$ levels of Z.

Create Age Categories

```
Rossi$age.cat <- cut(Rossi$age, c(0, 19, 25, 30, Inf))
xtabs(~age.cat, data = Rossi)
```

```
## age.cat
##   (0,19]  (19,25]  (25,30] (30,Inf]
##       66      236       66       64
```

Re Run the Model

```
mod2 <- coxph(Surv(week, arrest) ~ fin + race + mar + paro +
    prio + strata(wexp, age.cat), data = Rossi)
tidy2 <- tidy(mod2, exponentiate = T)
knitr::kable(tidy2[-c(3, 4)])
```

TERM	ESTIMATE	P.VALUE	CONF.LOW	CONF.HIGH
finyes	0.675	0.040	0.463	0.983
raceother	0.720	0.290	0.392	1.322
marnot married	1.462	0.326	0.686	3.117
paroyes	0.915	0.650	0.623	1.343
prio	1.084	0.004	1.026	1.146

PH Assumption

```
cox.zph(mod2)
```

```
##                       rho  chisq     p
## finyes         -0.0147 0.0252 0.874
## raceother       0.1086 1.3066 0.253
## marnot married -0.0794 0.8033 0.370
## paroyes        -0.0112 0.0141 0.906
## prio           -0.0174 0.0326 0.857
## GLOBAL              NA 2.3420 0.800
```

Influential Observations

- to test this let's build a smaller model

```
mod3 <- coxph(Surv(week, arrest) ~ fin + prio + strata(age.cat),
    data = Rossi)
```

Influential Observations

- With Cox PH we will use DFBETA to tell.
- DFBETA's measure how much an observation has effected the estimated coefficient.
- We look for values to be under $\frac{2}{\sqrt{n}}$.

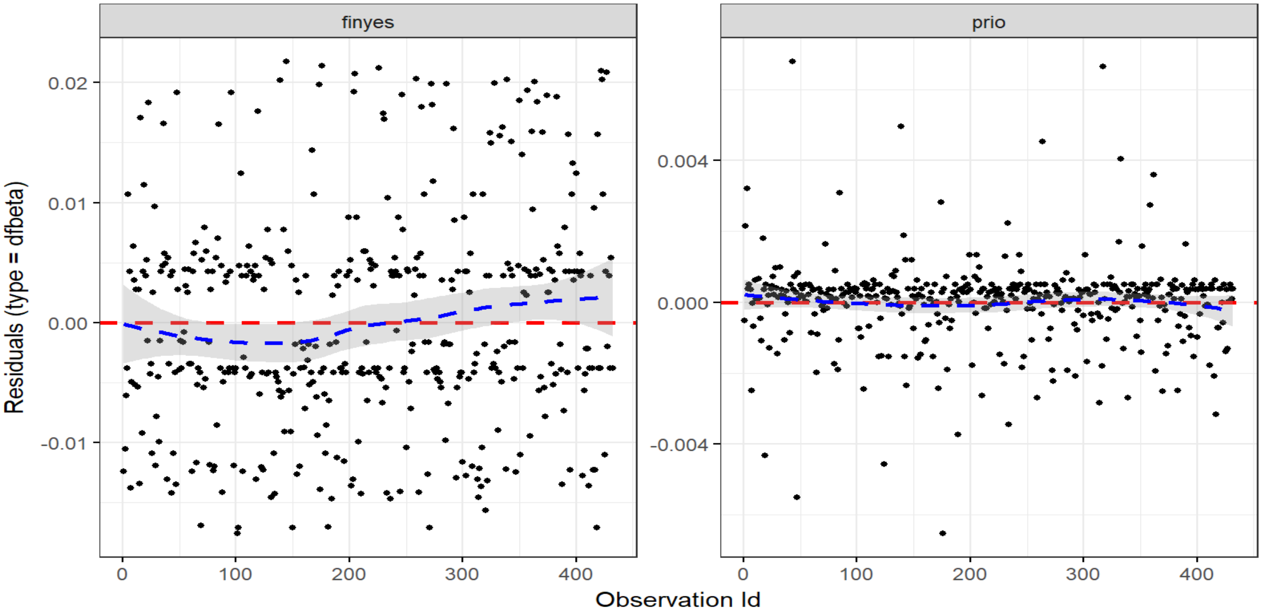
DFBETA in R

```
library(survminer)
2/sqrt(dim(Rossi)[1])
```

```
## [1] 0.0962
```

```
ggcoxdiagnostics(mod3, type = "dfbeta", linear.predictions = FALSE,
    ggtheme = theme_bw())
```

DFBETA in R


finyes
prio
Residuals (type = dfbeta)
0.02
0.01
0.00
-0.01
0.004
0.000
-0.004
0
100
200
300
400
Observation Id