Survival Analysis

Lecture 11

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Outline

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Stratified proportional hazard model

- an extension of the proportional hazard model allows for multiple strata
- the strata divide the individuals in disjoint groups $j, j = 1, \ldots, s$ each with a *different baseline hazard function* $h_{0j}(t)$ but with common values for the coefficients of the vector β
- the hazard function in the j stratum is

$$h_j(t \mid Z(t) = h_{0j}(t)\exp(\beta^\top \mathbf{Z}(t)), \quad j = 1, \ldots, s$$

- the overall loglikelihood becomes

$$LL(\beta) = \sum_{s=1}^{S} LL_s(\beta)$$

- $LL_s(\beta)$; log partial likelihood using only the data for those individuals in the s^{th} stratum
- the score vector and the information matrix are similar sums

$$U(\beta) = \sum_{s=1}^{S} U_s(\beta);\ \mathcal{I}(\beta) = \sum_{s=1}^{S} \mathcal{I}_s(\beta)$$

- the score vector and the information matrix make use of the weighted mean of the covariates of all subjects in *stratum s* who are still alive and at risk at time *t* and the weighted variance matric of those subjects
- analysis of multicenter clinical trials often uses stratification
- because of the different patient population the different center are likely to have different baseline survival curves
- in a Cox model the `strata` option is used to allow separate baseline hazards for subgroups of the data while retaining the common coefficients for the other covariate across groups

- the stratified Cox model can be obtained by using a strata directive within the fit

```
> data(ovarian)
> names(ovarian)
[1] "futime"   "fustat"   "age"        "resid.ds" "rx"
+   "ecog.ps"
```

- `futime`: number of days from enrollment until death or censoring
- `fustat`: indicator of death `(1)` or censoring `(0)`
- `age`: patient age in years (age in days divided by 365.25)
- `residual.dz`: indicator of the extent of residual disease
- `rx`: treatment given
- `ecog.ps`: measure of performance score or functional status; it ranges from `0` (fully functional) to `4` (completely disabled)

- code stratified Cox model

```
> fit <- coxph(Surv(futime, fustat) ~ age + ecog.ps + strata(rx),
+     data=ovarian)

Call:
coxph(formula = Surv(futime, fustat) ~ age + ecog.ps + strata(rx),
    data = ovarian)


             coef exp(coef) se(coef)      z      p
age        0.1385     1.149    0.048  2.885 0.0039
ecog.ps -0.0967     0.908    0.630 -0.154 0.8800

Likelihood ratio test=12.7  on 2 df, p=0.00174  n= 26
```

- advantage of stratification: it gives the most general adjustment for a confounding variable
- disadvantage: no direct estimate of the importance of the strata effect is produced (no *p*-value)

Outline

Checking model assumption

- determine whether a fitted Cox regression model adequately describes the data
- Two basic assumptions of the Cox model are *log-linearity* and *proportional hazards*
- *log-linear* model (implies that the log of the hazard is assumed to change linearly with any continuous predictors)

$$\log[h(t|\mathbf{Z}(t))] = \log(h_0(t)) + \sum_{k=1}^{p} \beta_k Z_k(t)$$

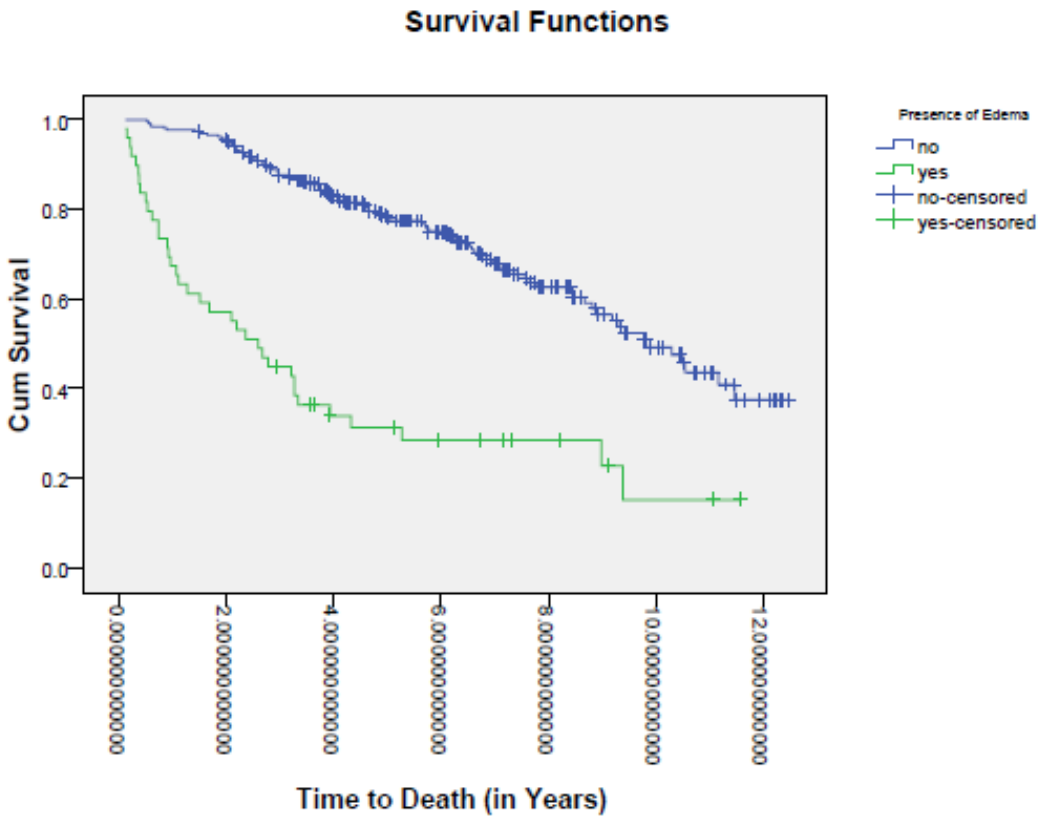
- a workable method for assessing violations of log-linearity is to use more complicated models for improvements in fit
- for example: add polynomial terms in the predictor in question to the model and then check effect sizes and P-values to determine whether the higher order terms are important

Pbc data

- a cohort of 312 participants in a placebo-controlled clinical trial of D-penicillamine (DPCA) for primary biliary cirrhosis (PBC) (Dickson et al., 1989)
- PBC destroys bile ducts in the liver, causing bile to accumulate
- Tissue damage is progressive and ultimately leads to liver failure
- Time from diagnosis to end-stage liver disease ranges from a few months to 20 years
- During the approximate ten year follow-up period, 125 study participants died

```
> # data is a SPSS file
> library(foreign)
> pbc <- read.spss("pbc.sav",use.value.labels=FALSE,
to.data.frame=TRUE)
> names(pbc)
 [1] "number"    "status"    "rx"        "sex"       "asictes"
 [6] "hepatom"   "spiders"   "edema"     "bilirubin" "cholest"
[11] "albumin"   "copper"    "alkphos"   "sgot"      "trigli"
[16] "platel"    "prothrom"  "histol"    "age"       "years"
[21] "logbili"   "logalbu"   "logprot"
```

- Estimate Kaplan-Meier curve with variable edema as factor



- By looking at the Kaplan-Meier curve do you think the proportional hazards assumption is fulfilled?

- The log rank test is significant
- By looking at the plot, we can say that the proportional hazard assumption might not be true
- The plot shows shorter survival in patients with edema at baseline
- The stratum-specific survival functions also suggest that the multiplicative effect of edema on the mortality hazard is not constant over time

- model the effect of edema among patients with PBC in the DPCA cohort
- use the binary predictor `edema`, coded `1` for patients with edema and `0` for others
- unadjusted model the hazard for patients with edema

$$h(t|Z) = h_0(t)\exp(\beta)$$

- and without edema $h_0(t)$
- the hazard for patients with edema is modeled as a constant proportion $\exp(\beta)$ of the baseline hazard $h_0(t)$

- later we shall see that the proportional hazard assumption does not hold for `edema`
- accommodate the violations by fitting a stratified Cox model in which separate baseline hazard are used for patients with and without edema

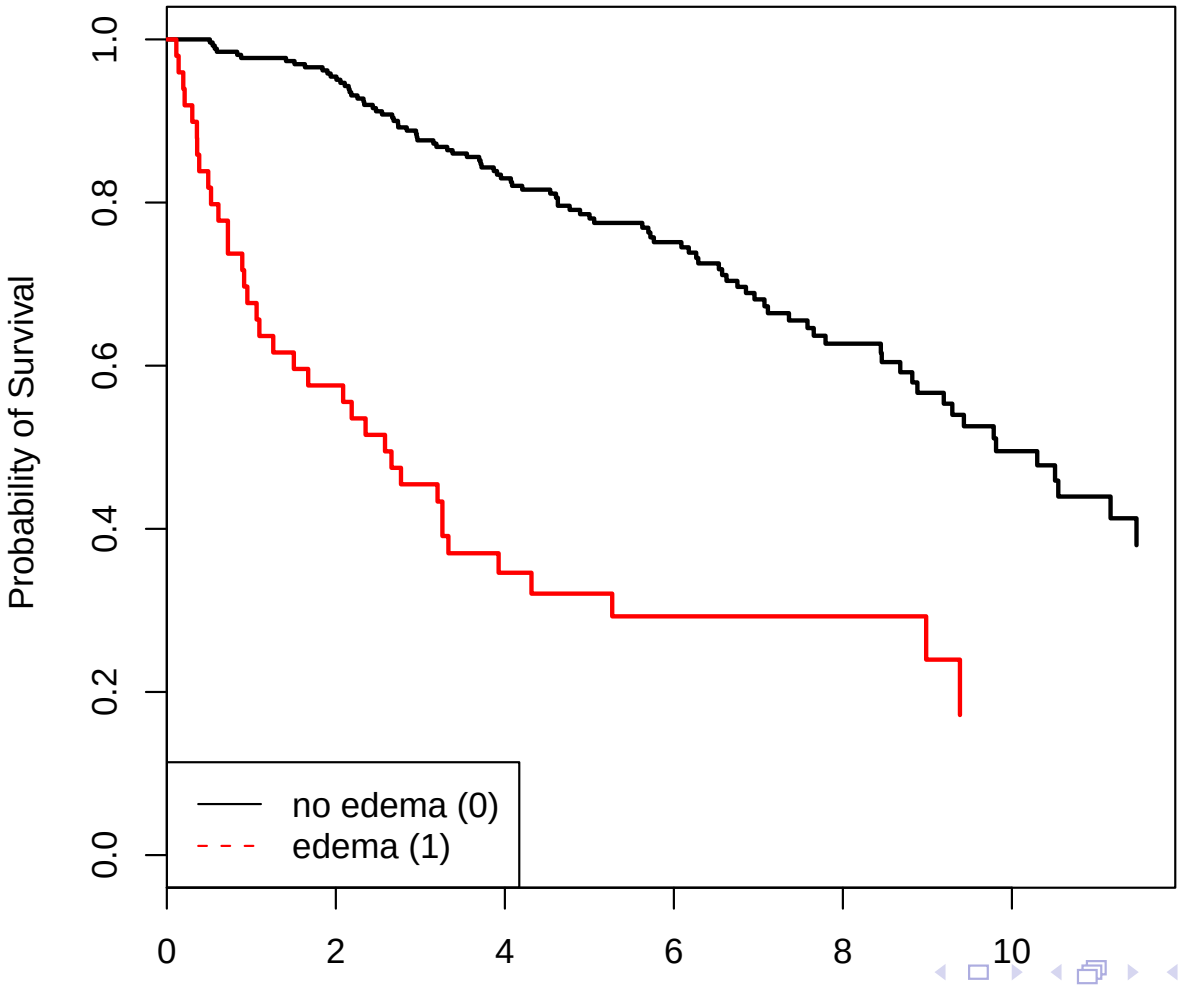
$$h(t|edema = 1) = h_{01}(t)$$

$$h(t|edema = 0) = h_{00}(t)$$

- Fit a Cox model with edema as stratifying variable

```
res <- coxph(Surv(years, status)~strata(edema), data=pbc)
plot(survfit(res), col=1:2, lwd=2,xlab="Years since enrollment",
ylab ="Probability of Survival")
legend("bottomleft", legend=c("no edema (0) ", "edema (1)"),
lty=c(1,2),col=c("black", "red") )
```

Stratified survival curves



- stratified, adjusted survival curves can give a clear visual impression of the effect of the stratification variable after adjustment
- current methods for the stratified Cox model do not allow us to estimate or test the statistical significance of its effect
- stratification could be used in our example to adjust for edema, but might be less useful if edema were a predictor of primary interest
- time-dependent covariates can be used to obtain valid estimates of the effects of a predictor which violates the proportional hazards assumption

compare survival curves according to edema adjusting for age

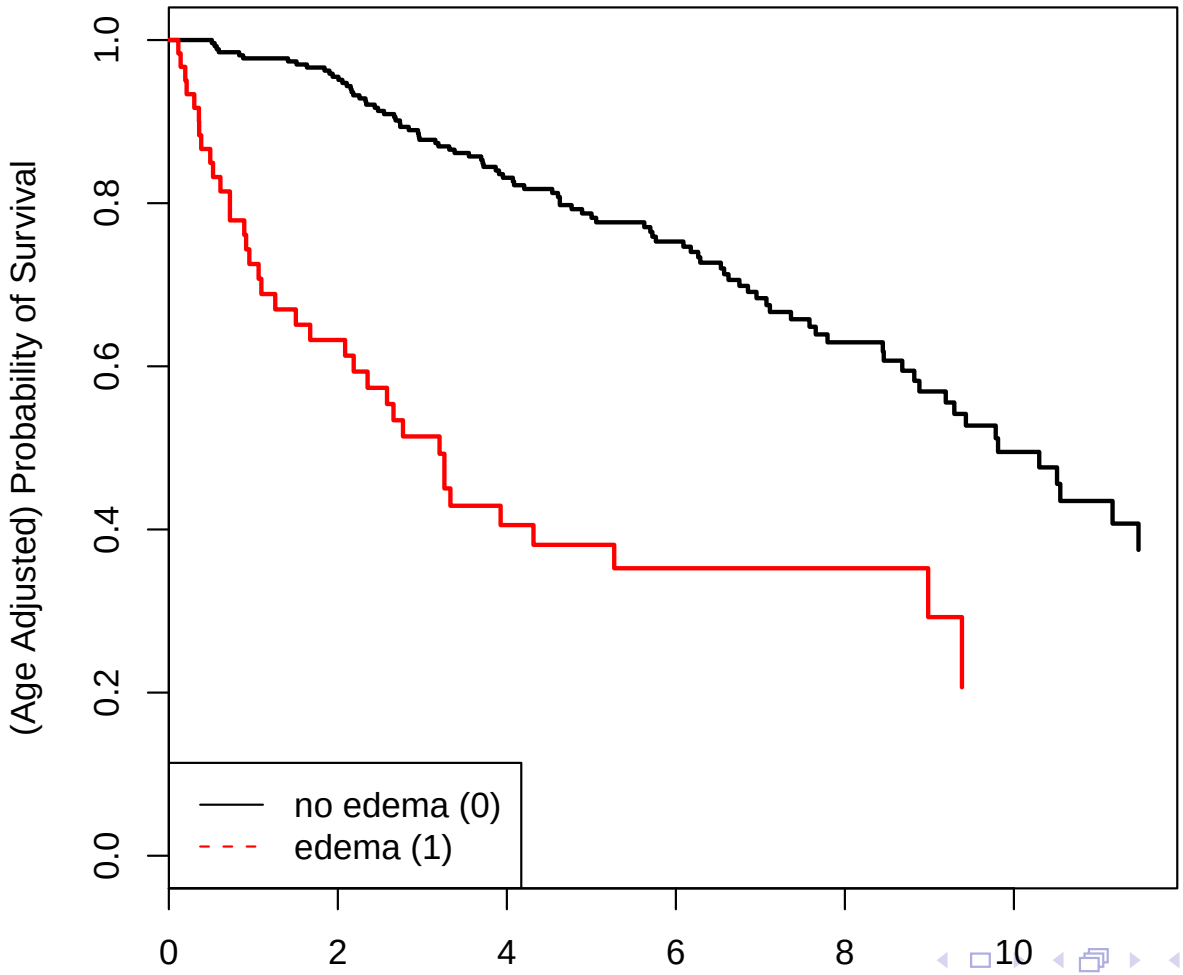
```
>  res <- coxph(Surv(years, status)~age + strata(edema),
        data=pbc)

> plot(survfit(res), col=1:2, lwd=2,xlab="Years since enrollment",
  ylab ="(Age Adjusted) Probability of Survival")
 legend("bottomleft", legend=c("no edema (0) ", "edema (1)"),
 lty=c(1,2),col=c("black", "red") )
```

- under the stratified Cox model the survial function for a PBC subject with centered `age` is given by

$$[S_{0j}(t)]^{\exp(\beta_{age})}$$

Stratified survival curves for edema adjusted for age



- The adjusted survival curves for the edema ($j = 1$) and no edema ($j = 0$) strata, adjusted to age 50 ((mean(age)=50)), are therefore $S_{01}(t)$ and $S_{00}(t)$ respectively
- we see shorter survival in patients with edema at baseline
- these stratum-specific survival functions also suggest that the multiplicative effect of edema on the mortality hazard is not constant over time
- the plot suggests that edema may violate the proportional hazards assumption: the increase in risk is greatest in the first few years and then diminishes
- the effect of edema on the hazard is time-dependent
- transform the survival plot to look at possible violations of the proportional hazards assumption

Log-minus-Log survival plots

- If proportional hazards hold for `edema` then

$$S_1(t) = [S_0(t)]^{\exp(\beta)}$$

- $S_0(t)$: survival function for patients without `edema=0`
- $S_1(t)$: survival function for patients with `edema=1`
- the *log-minus-log* transformation gives

$$\log(-\log[S_1(t)]) = \beta + \log(-\log[S_0(t)])$$

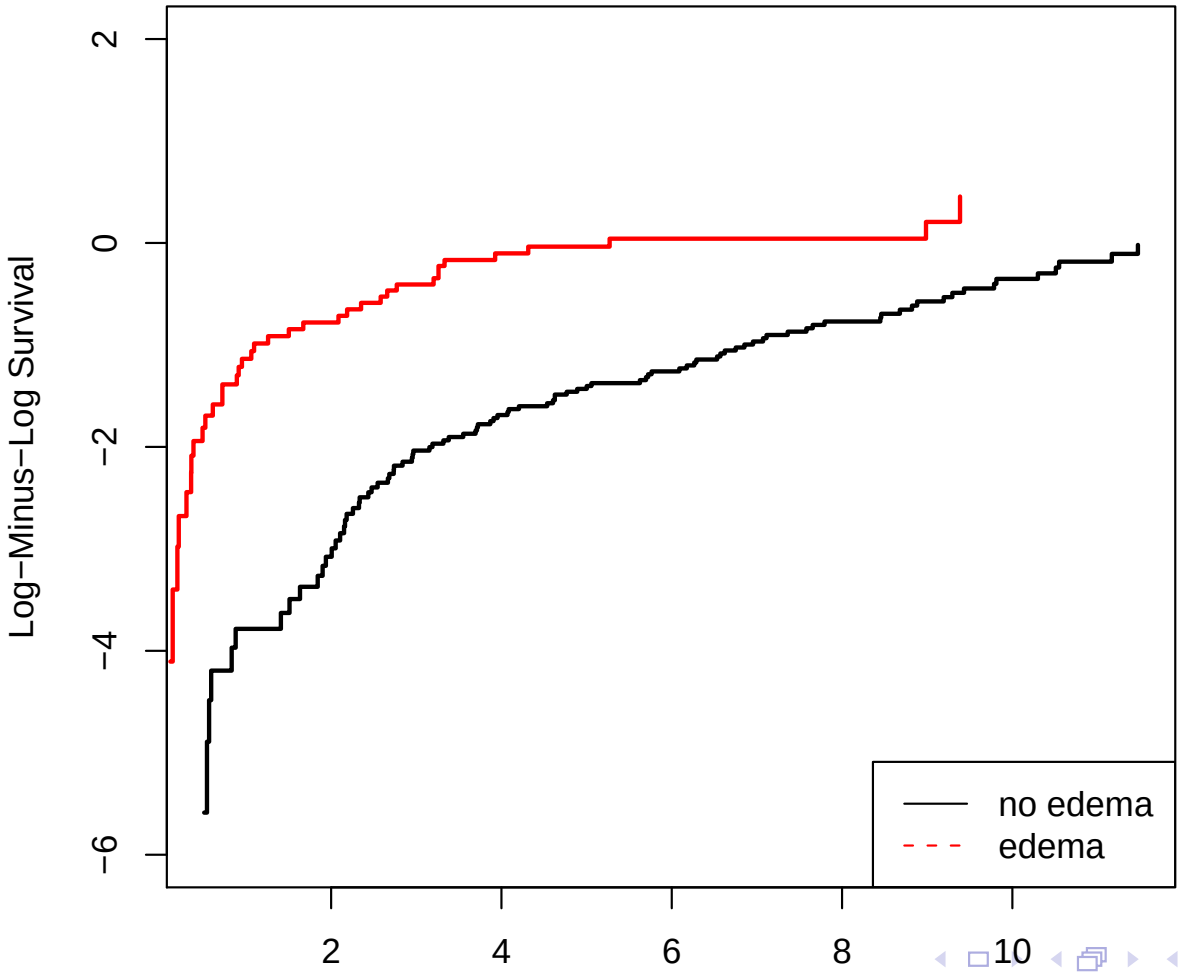
- when proportional hazards holds, the two transformed survival functions will be a constant distance β apart, where β is the log of the hazard ratio
- use a graphical method for examining the proportional hazards assumption

plot *Log-minus-Log* survival

```
>  res <- coxph(Surv(years, status)~age + strata(edema), data=pbc)
>  res1 <- summary(survfit(res))
> res1$strata
    88 edema=0; 34: edema=1

> plot(res1$time[1:88], log(-log(res1$surv[1:88])),type="s",lwd=2,
              ylim=c(-6,2), xlab="Years since enrollment",
              ylab="Log-Minus-Log Survival")
> lines(res1$time[89:122], log(-log(res1$surv[89:122])),type="s",
      lwd=2, col="red")
> legend("bottomright", legend=c("no edema ", "edema "), lty=c(1,2),
      col=c("black", "red") )
```

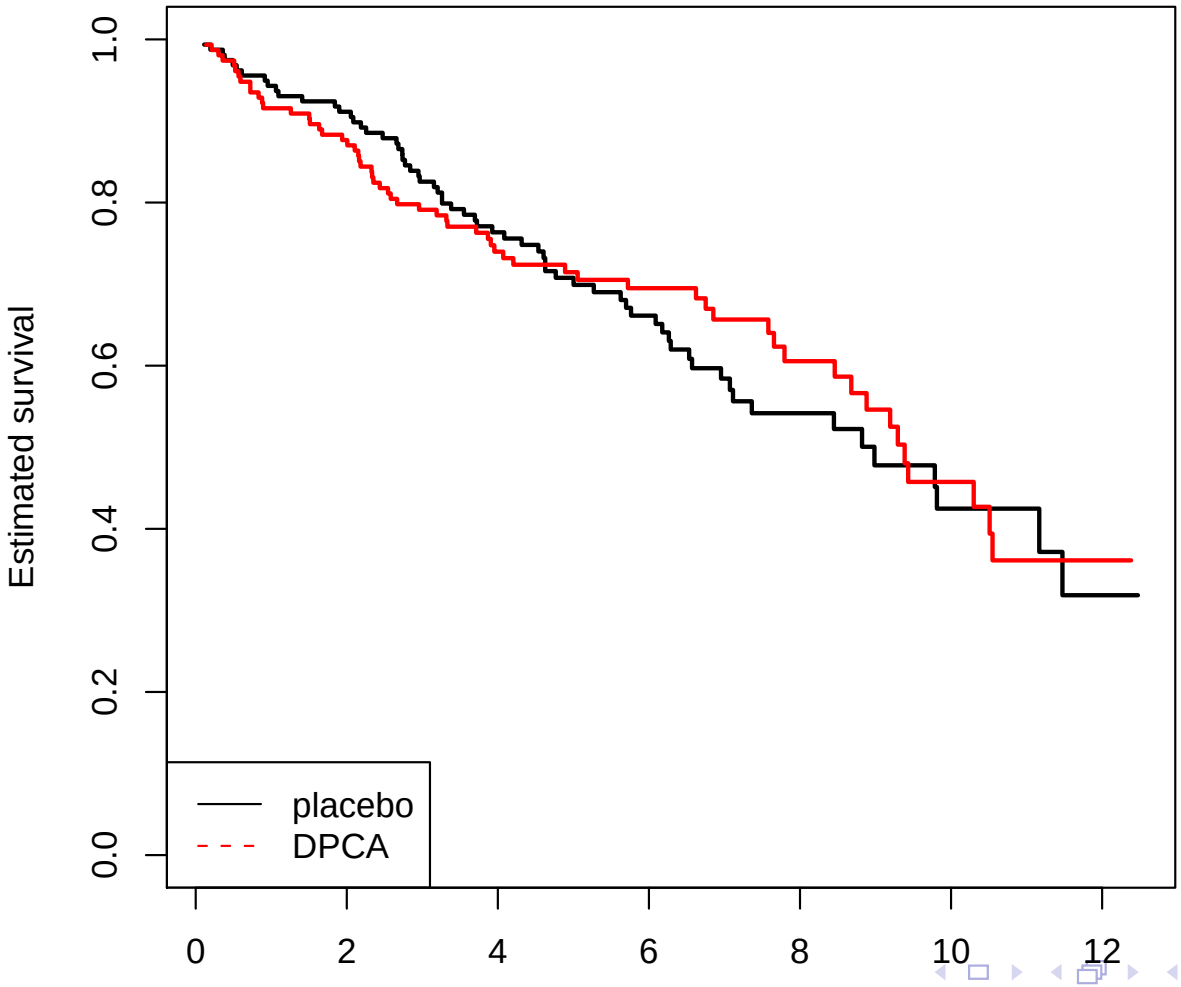
Log-minus-Log survival plot for edema



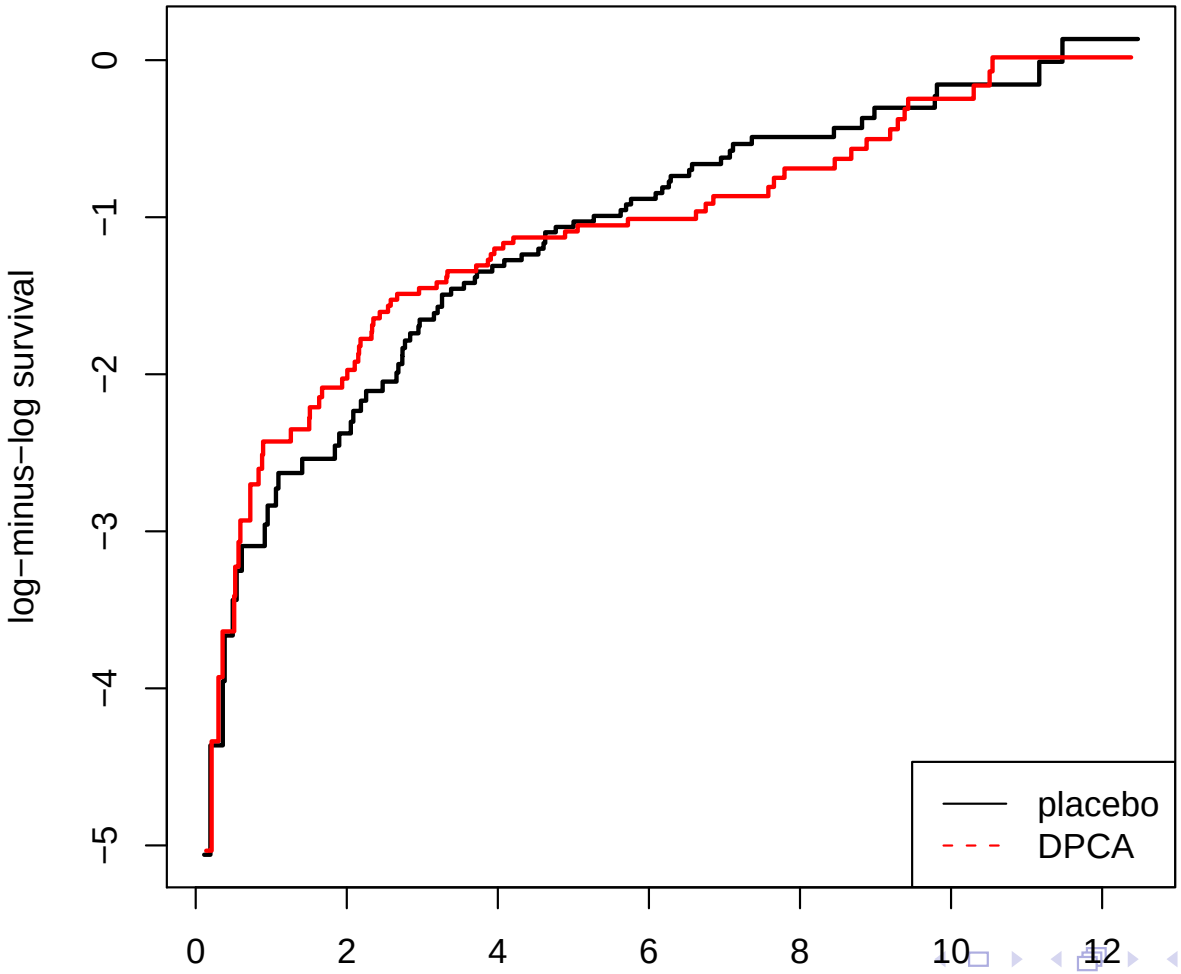
- the plot shows clear evidence of a violation of proportionality
- there is a big difference between the groups at all time points: patients with edema have poorer survival
- the difference between the groups diminishes with follow-up
- the distances between the curves (the implied log hazard ratios) are: 4.7, 1.8, 1.1, and 1.0 at years 1, 4, 7, and 10, respectively

- consider now the treatment indicator (`rx`) in the DPCA trial
- repeat the same analysis as with `edema` but now stratify on `rx`
- plot the survival for the stratified Cox model
- plot *Log-minus-Log* survival for Treatment
- code as before but now `strata(rx)`

Survival stratified curves for treatment



Log-minus-Log survival plot for treatment



- the curves for DPCA and placebo remain close over the entire follow-up period and do not suggest non-proportionality
- in assessing the *log-minus-log* survival plot for evidence of non-proportionality, the patterns to look for are: convergence, divergence, or crossing of the curves followed by divergence
- convergent curves suggest that the difference between the groups decreases with time, and vice versa
- if the curves converge, cross, and then diverge, then the non-proportionality may be more important; for example, this might indicate that treatment is harmful early on but protective later

Outline

Checking Proportional Hazards by using residuals

- Tests for proportional hazards are based on rescaled Schoenfeld residuals and can be obtained with `cox.zph`
- Schoenfeld residuals are defined as a matrix

$$s_{ij}(\beta) = Z_{ij}(t_i) - \bar{Z}_j(\beta, t_i)$$

- with one row per death time and one column per covariate; i, t_i: subject and time that the event occurred (j: variable)
- the `cox.zph` function calculates tests of the proportional-hazards assumption for each covariate, by correlating the corresponding set of scaled Schoenfeld residuals with a suitable transformation of time

- it has been proved (Grambsch & Therneau) that

$$E(s_{ij}^*) + \hat{\beta}_j \approx \beta_j(t_i),$$

- s_{ij}^*: scaled Schoenfeld residuals
- this suggests plotting $s_{ij}^* + \hat{\beta}_j$ versus time, or some function of time $g(t)$ as a method to visualize the nature of the nonproportional hazard; $s_{ij}^* = V^{-1}(\hat{\beta}, t_i)s_i$ (s_i: Schoenfeld residual for the i^{th} event)
- a line can be fit to the plot followed by a test for zero slope
- a non zero slope is evidence against proportional hazard
- tests for the proportional-hazards assumption are obtained from `cox.zph` in the survival package

Outline

- use data on recidivism to illustrate the function
- fit Cox model but eliminate the covariates whose coefficients are not statistically significant

```
> res <- coxph(Surv(week, arrest) ~ fin + age + prio ,
data=Rossi)
> res
Call:
coxph(formula = Surv(week, arrest) ~ fin + age + prio,
 data = Rossi)


        coef exp(coef) se(coef)     z       p
fin  -0.3470     0.707   0.1902 -1.82 0.06800
age  -0.0671     0.935   0.0209 -3.22 0.00130
prio  0.0969     1.102   0.0273  3.56 0.00038

Likelihood ratio test=29.1  on 3 df, p=2.19e-06  n= 432
```

- tests for the proportional-hazards assumption are obtained from `cox.zph`
- `cox.zph` computes a test for each covariate, along with a global test for the model as a whole

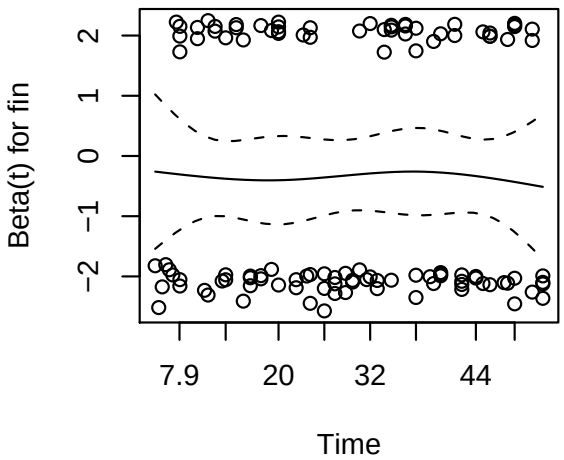
```
> cox.zph(res)
          rho    chisq       p
fin    -0.00657 0.00507 0.9433
age    -0.20976 6.54147 0.0105
prio   -0.08004 0.77288 0.3793
GLOBAL       NA 7.13046 0.0679
```

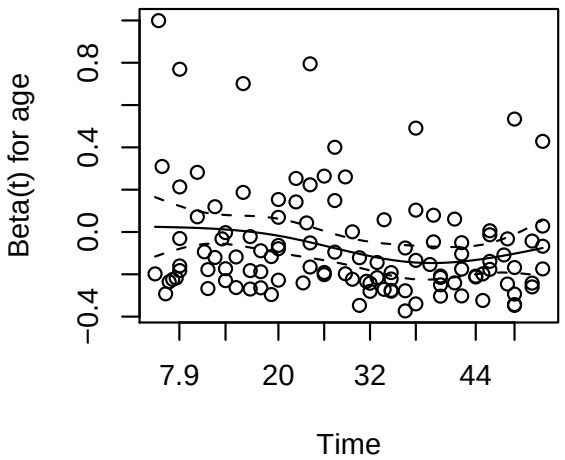
- ρ: correlation coefficient between survival time and the Schoenfeld residuals
- there is strong evidence of non-proportional hazards for age
- the global test (on 3 degrees of freedom) is not quite statistically significant

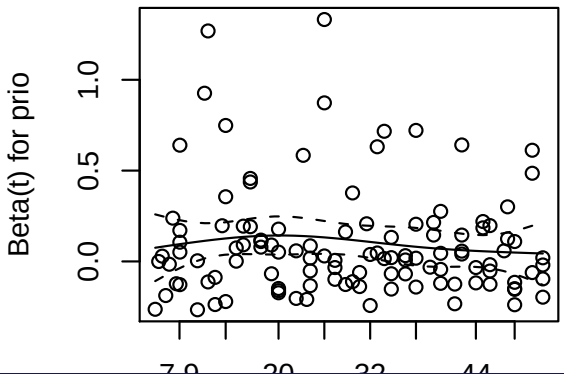
- Plotting the object returned by `cox.zph` produces graphs of the scaled Schoenfeld residuals against transformed time

```
> par(mfrow=c(2,2))
> plot(cox.zph(res))
```

Plots of scaled Schoenfeld residuals; solid line is a smoothing-spline fit to the plot (dotted lines represent a confidence band around the fit)







- `cox.zph` uses a smoothing spline, shown on each graph by a solid line
- Systematic departures from a horizontal line are indicative of non-proportional hazards
- the assumption of proportional hazards appears to be supported for the covariates `fin` (financial aid after release of prison) `prio` (number of prior convictions)
- there is a trend in the plot for `age` with the age effect declining with time (this effect was detected in the test reported above)

- One way of accommodating non-proportional hazards is to build interactions between covariates and time into the Cox regression model
- such interactions are themselves time-dependent covariates
- based on the diagnostics just seen, it seems reasonable to consider a linear interaction of time and age
- we can use the data frame constructed before (Rossi2) and again fit a cox model

```
> res <- coxph(Surv(start, stop, arrest.time) ~ fin + age +
        age:stop + prio, data=Rossi.2)
> res
Call:
coxph(formula = Surv(start, stop, arrest.time) ~ fin + age +
    age:stop + prio, data = Rossi.2)


              coef exp(coef) se(coef)      z       p
fin       -0.34856     0.706  0.19023 -1.832 0.06700
age        0.03228     1.033  0.03943  0.819 0.41000
prio       0.09818     1.103  0.02726  3.602 0.00032
age:stop -0.00383     0.996  0.00147 -2.612 0.00900

Likelihood ratio test=36  on 4 df, p=2.85e-07  n= 19809
```

- the coefficient for the interaction is negative and highly significant; the effect of age declines with time
- initially, age has a positive partial effect on the hazard ($\hat{\beta}_{age} = 0.032$), but this effect gets smaller with time (at the rate $\hat{\beta}_{age:stop} = -0.0038$ per week)

- alternative: fit a stratified Cox model on *age*
- advantage: not necessary to assume a particular form of interaction
- create categories for covariate age: 19 or younger; 20-25; 26- 30; 31 or older (use for example function `recode` from library *car*)

```
> library(car)
> Rossi$age.cat <- recode(Rossi$age, " lo:19=1; 20:25=2;
                  26:30=3;  31:hi=4 ")
> table(Rossi$age.cat)

 1   2   3   4
66 236  66  64
```

```
> res<- coxph(Surv(week, arrest) ~fin + prio + strata(age.cat),dat
> res
Call:
coxph(formula = Surv(week, arrest) ~ fin + prio + strata(age.cat),
    data = Rossi)


       coef exp(coef) se(coef)     z      p
fin  -0.341     0.711    0.190 -1.79 0.0730
prio  0.094     1.099    0.027  3.48 0.0005

Likelihood ratio test=13.4  on 2 df, p=0.00122  n= 432
> cox.zph(res)
           rho  chisq     p
fin    -0.0183 0.0392 0.843
prio   -0.0771 0.6859 0.408
GLOBAL      NA 0.7299 0.694
```

- there is no evidence of non-proportional hazards for the other covariates