Survival analysis:
Time dependent covariates

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Roadmap

- Background
- Piecewise Cox models
- The Stanford heart transplant data

Background

- Tests for the proportional hazards assumption
  1. Plot $\log[-logS(t)]$ as a function of time for each strata of the explanatory variable: if the CPH assumption is valid curves should be approximately parallel
  2. Introduce a time-dependent interaction term for the explanatory variable: if CPH assumption valid the addition of the interaction term *won't* be significant [more later]
  3. Plot Schoenfeld residuals *vs* time: if CPH assumption valid Schoenfeld residuals should be scattered around 0 and have slope of 0

Background

What we're talking about here is when the <u>effect</u> of a covariate changes over time

- Methods for dealing with non proportional hazards
  1. Stratification
  2. Time-dependent covariates

- How do we handle the situation when the <u>explanatory variable itself</u> changes over time?
  - repeated measurements on a subject
  - change in a subject's treatment

Roadmap

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- <u>Piecewise Cox models</u>
- The Stanford heart transplant data

Piecewise Cox models

- Explanatory variables that change over time
  - the survival period for each individual is divided up into a sequence of shorter 'survival spells', each characterised by an entry and an exit time, and within which covariate values remain fixed
  - take the `addict` data set and suppose that the dose of methadone is reduced by 50% after 365 days into the program

id	start	stop	status	clinic	prison	dose
1	0	365	0	1	0	50
1	365	428	1	1	0	25
2	0	275	1	1	1	55
3	0	262	1	1	0	55
4	0	183	1	1	0	30
5	0	259	1	1	1	65

Piecewise Cox models

- This approach is called the step function proportional hazards or piecewise Cox model

- In each interval
  - subjects who are censored or die during the interval are treated as usual (coded as censored or died)
  - subjects who live through the interval to the next are censored at the end of the interval

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Piecewise Cox models

- A concern is that the observations, when organised in this way, are ‘correlated’ (implying that something needs to be done about that correlation)
  - not an issue, since the partial likelihood on which estimation is based has a term for each unique death or event time, and involves sums over those observations that are available or at risk at the actual event date
  - since the intervals for a particular individual don’t overlap, the likelihood will involve at most only one observation for an individual

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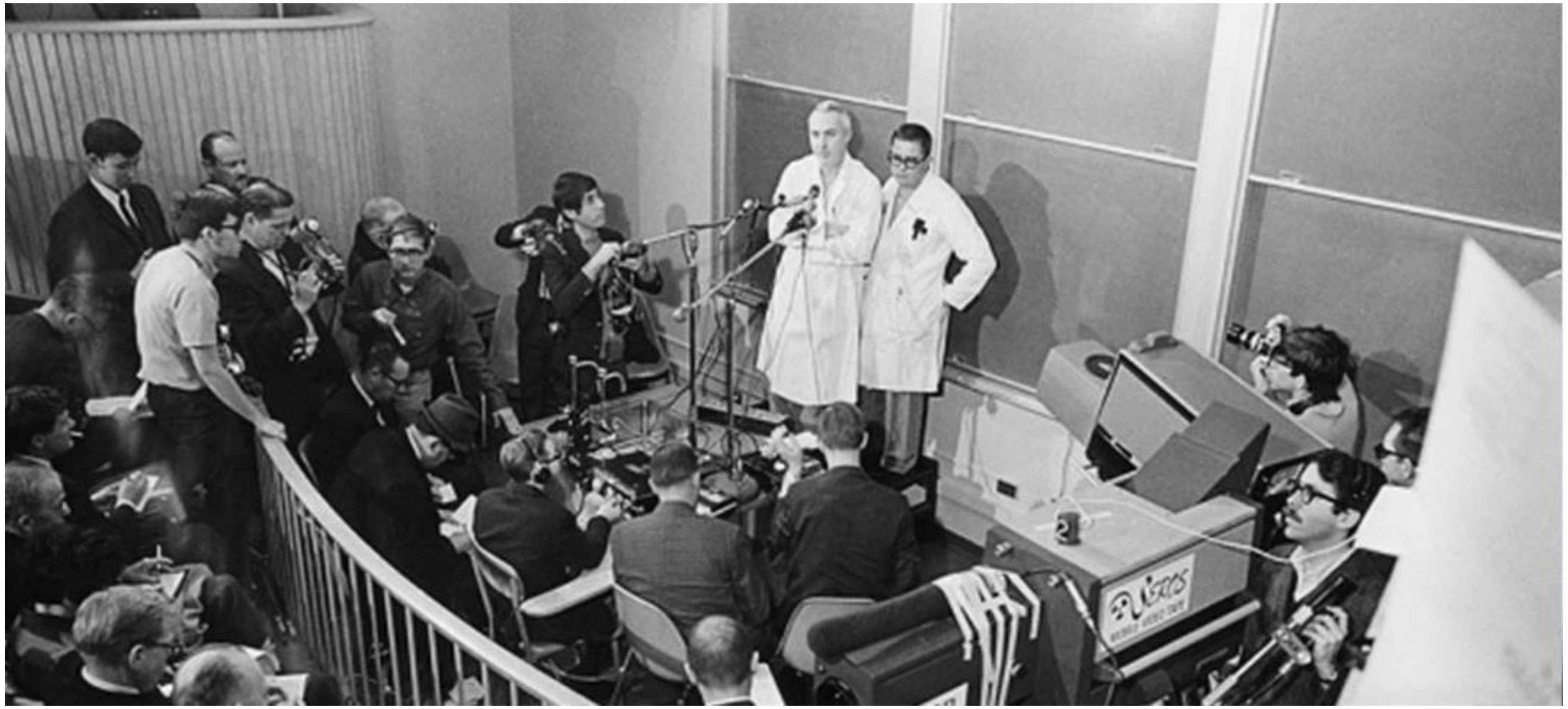

The Stanford heart transplant data

- Stanford heart transplant study
  - the question: did patients who received heart transplants during the early days of the program live longer than those that didn't?

    Reference: Crowley J and Hu M (1977) Covariance analysis of heart transplant data. Journal of the American Statistical Association 78: 277 - 281.

```
library(survival); setwd("D:\\TEMP");
dat <- read.table("heart.csv", header =
head(dat);

id start stop event        age      year
1      0   50     1 -17.155373 0.1232033       0       0
2      0    6     1   3.835729 0.2546201       0       0
3      0    1     0   6.297057 0.2655715       0       0
3      1   16     1   6.297057 0.2655715       0       1
4      0   36     0  -7.737166 0.4900753       0       0
4     36   39     1  -7.737166 0.4900753       0       1

id: patient identifier.
start: days from entry into program.
stop: days from entry into program to event.
event: 0 = censored, 1 = died.
age: age in years minus 48.
year: date accepted into the program (years from 1 Oct 1967).
surgery: 0 = no previous surgery, 1 = previous surgery.
transplant: 0 = no transplant, 1 = transplant.
```

Entered the program on day 0 and died,

Entered the program on day 0 and died.

Entered the program on day 0, spent 1 day on the waiting list and was then transplanted. Died 16 days later.

The Stanford heart transplant data

- Method 1: stratify by transplant status

```
heart.cph01 <- coxph(Surv(start, stop, event) ~ age + surgery +
strata(transplant), data = dat, method = "breslow");
summary(heart.cph01);
```

```
Call:
coxph(formula = Surv(start, stop, event) ~ age + surgery +
strata(transplant), data = dat, method = "breslow")

  n= 172
           coef exp(coef) se(coef)     z
age      0.0321     1.033   0.0141  2.28
surgery -0.7678     0.464   0.3619 -2.12

        exp(coef) exp(-coef) lower .95 upper .95
age         1.033      0.968     1.005     1.062
surgery     0.464      2.155     0.228     0.943

Rsquare= 0.062   (max possible= 0.953 )
Likelihood ratio test= 10.9  on 2 df,   p=0.00422
Wald test            = 9.85  on 2 df,   p=0.00725
Score (logrank) test = 10.2  on 2 df,   p=0.0061
```

Cardiac surgery before acceptance into the program decreased the daily hazard of death by 0.45 (95% CI 0.23 – 0.94).

The Stanford heart transplant data

- Method 1: stratify by transplant status
- Method 2: transplant status as a time dependent covariate (age and surgery as explanatory variables)

```r
options(contrasts = c("contr.treatment", "contr.poly"));
heart.cph02 <- coxph(Surv(start, stop, event) ~ (age + surgery) *
transplant, data = dat, method = "breslow");
summary(heart.cph02);
```

```
                     coef exp(coef) se(coef)      z    p
age                0.0138     1.014   0.0181  0.763 0.45
surgery           -0.5457     0.579   0.6109 -0.893 0.37
transplant         0.1181     1.125   0.3277  0.360 0.72
age:transplant     0.0348     1.035   0
surgery:transplant -0.2916     0.747   0

                   exp(coef) exp(-coef)
age                    1.014      0.986
surgery                0.579      1.726
transplant             1.125      0.889      0.592      2.14
age:transplant         1.035      0.966      0.982      1.09
surgery:transplant     0.747      1.339      0.169      3.30

Rsquare= 0.07   (max possible= 0.969 )
Likelihood ratio test= 12.4  on 5 df,   p=0.0291
Wald test            = 11.6  on 5 df,   p=0.0402
Score (logrank) test = 12.0  on 5 df,   p=0.0345
```

For transplanted patients, unit increases in age

For transplanted patients, cardiac surgery before acceptance into the program decreased the daily hazard of death by 0.75 (95% CI 0.17 – 3.30).

The Stanford heart transplant data

- Method 1: stratify by transplant status
- Method 2: transplant status as a time dependent covariate (age and surgery as explanatory variables)
- Method 3: transplant status as a time dependent covariate (age and year as explanatory variables)

```r
heart.cph03 <- coxph(Surv(start, stop, event) ~ (age + year) *
transplant, data = dat, method = "breslow");
summary(heart.cph03);
```

```
                    coef exp(coef) se(coef)      z      p
age               0.0155     1.016   0.0173  0.895 0.3700
year             -0.2735     0.761   0.1058 -2.585 0.0097
transplant       -0.5884     0.555   0.5427 -1.084 0.2800
age:transplant    0.0339     1.034   0.0279  1.211 0.2300
year:transplant   0.2013     1.223   0.1425  1.413 0.1600

                 exp(coef) exp(-coef) lower .95 upper .95
age                  1.016      0.985     0.982     1.051
year                 0.761      1.315     0.618     0.936
transplant           0.555      1.801     0.192     1.609
age:transplant       1.034      0.967     0.979     1.093
year:transplant      1.223      0.818     0.925     1.617

Rsquare= 0.083   (max possible= 0.969 )
Likelihood ratio test= 14.8  on 5 df,   p=0.0111
Wald test            = 13.8  on 5 df,   p=0.0172
Score (logrank) test = 14.0  on 5 df,   p=0.0153
```

Variable	Coefficient (SE)	P	Hazard ratio (95%)
Age	0.0155 (0.0173)	0.37	1.02 (0.98 – 1.05)
Year	-0.2735 (0.1058)	<0.01	0.76 (0.62 – 0.94)
Transplant	-0.5884 (0.5427)	0.28	0.55 (0.19 – 1.61)
Age × transplant	0.0339 (0.0279)	0.23	1.03 (0.98 – 1.09) [a]
Year × transplant	0.2013 (0.1425)	0.16	1.22 (0.92 – 1.62)

[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

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Unit increases in age at time of entry into the program increased the hazard of death by a factor of 1.02.

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Transplant	-0.5884 (0.5427)	0.28	0.55 (0.19 – 1.61)
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[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

With advancing years the hazard of death decreased once patients were accepted into the program. Implies an ↑ in patient 'quality' over time.

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Over the entire study period transplantation had a beneficial effect on survival.

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[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

For transplanted patients, unit increases in age at time of acceptance into the program was associated with an increased hazard of death.

Variable	Coefficient (SE)	P	Hazard ratio (95%)
Age	0.0155 (0.0173)	0.37	1.02 (0.98 – 1.05)
Year	-0.2735 (0.1058)	<0.01	0.76 (0.62 – 0.94)
Transplant	-0.5884 (0.5427)	0.28	0.55 (0.19 – 1.61)
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[a] Interpretation: compared with the reference category (patients that didn't receive a transplant) unit increases in age for transplanted patients increased the daily hazard of death by 1.03 (95% CI 0.98 – 1.09).

But as time progressed transplanted patients had an increased hazard of death. Survival of transplanted patients was not improving at the same rate as patient quality.

The Stanford heart transplant data

- Plot the expected survival curve for someone who was
  - 50 years of age when accepted into the program
  - had prior cardiac surgery
  - was on the transplant waiting list for 6 months

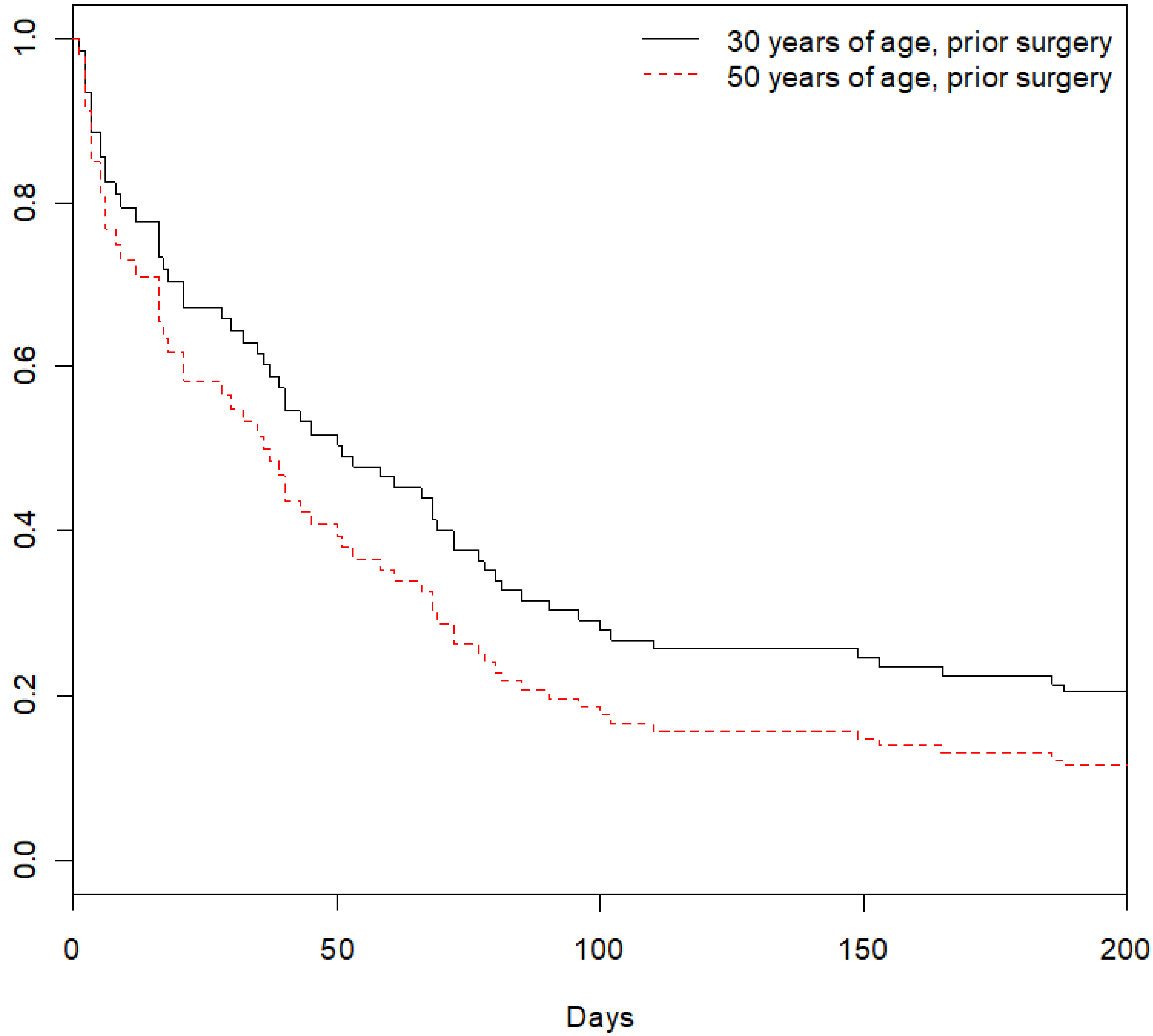
```
age30.dat <- data.frame(start = 0, stop = 183, age = 30 - 48, year =
0, surgery = 1, transplant = 0)
age50.dat <- data.frame(start = 0, stop = 183, age = 50 - 48, year =
0, surgery = 1, transplant = 0)
head(age50.dat)

start  stop   event  age year surgery transplant
0      183    1      -18    0       1          0
0      183    1        2    0       1          0

surv30 <- survfit(heart.cph03, newdata = age30.dat, individual =
FALSE, se = FALSE)
surv50 <- survfit(heart.cph03, newdata = age50.dat, individual =
FALSE, se = FALSE)
```

```
plot(surv30, lwd = 1, lty = 1, xlim = c(0, 200), xlab = "Days")
lines(surv50, lwd = 1, lty = 2, type = "s", col = "red")
legend(x = "topright", legend = c("30 years of age, prior surgery",
"50 years of age, prior surgery"), col = c("black", "red"), lwd =
c(1,1), lty = c(1,2), bty = "n")
```

Stanford heart transplant data (Crowley and Hu 1977). Predicted survival curve for a patient of 30 years at time of entry into the transplant program and a patient 50 years of age at time of entry.



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