Introduction

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Frailty models: Theory & Practice
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Outline

This course

Frailty models: Theory & Practice

- Introduction
- Univariate frailties
- Shared frailty models
- Computer practical
- Extensions and applications

This course

A little bit on how we will work

- Emphasis in first half on concepts
- In second half on practice
  - Discussion of software
  - Computer practical
- We like to keep things informal
  - Please interrupt, ask questions

Survival analysis

- Quote from Odd Aalen: “it takes time to observe time”
- Most important consequence
  - (Right) censoring: event has not (yet) occurred

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Random variables

- Two random variables
  - $\tilde{T}$: Survival time
  - C: Censoring time
- Assumption: $\tilde{T}$ and C are independent
  - Possibly conditional on explanatory variables

Distribution and survival functions

- Cumulative distribution functions

$$\begin{aligned} F(t) &= P(\tilde{T} \leq t) \\ G(t) &= P(C \leq t) \end{aligned}$$

- $F(t)$ often called "(cumulative) incidence function", "distribution function" or "failure function"
- More common to use the complimentary survival and censoring functions

$$\begin{aligned} S(t) &= 1 - F(t) = P(\tilde{T} > t)\,, \\ \overline{G}(t) &= 1 - G(t) = P(C > t)\,. \end{aligned}$$

- Assumption: S and G continuous (only to make notation easier)

Observations

- For $i = 1, \ldots, n$, we observe realizations (t_i, d_i, x_i) of
  - $T_i = \min(\tilde{T}_i, C_i)$
  - $D_i = \mathbf{1}\{\tilde{T}_i \leq C_i\}$
  - X_i: p-vector of covariates
- Interest is in
  - Estimating survival probabilities based on these data
  - Quantifying the effects of covariates on these probabilities

Hazard

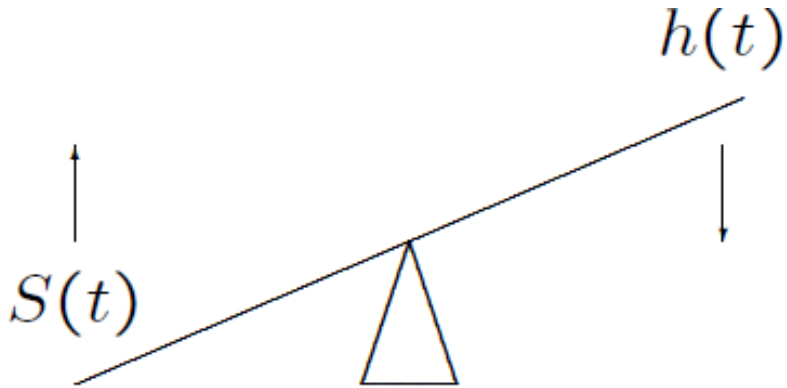
- Hazard function $h(t)$; event probability *at* t, given event-free until t

$$h(t) = \lim_{dt \to 0} \frac{P(t \leq \tilde{T} < t + dt \mid \tilde{T} \geq t)}{dt} \approx \frac{P(\tilde{T} = t)}{P(\tilde{T} \geq t)}$$

- Crucial to understand that the hazard function describes the randomness of the survival time

Qualitative relation between survival and hazard function

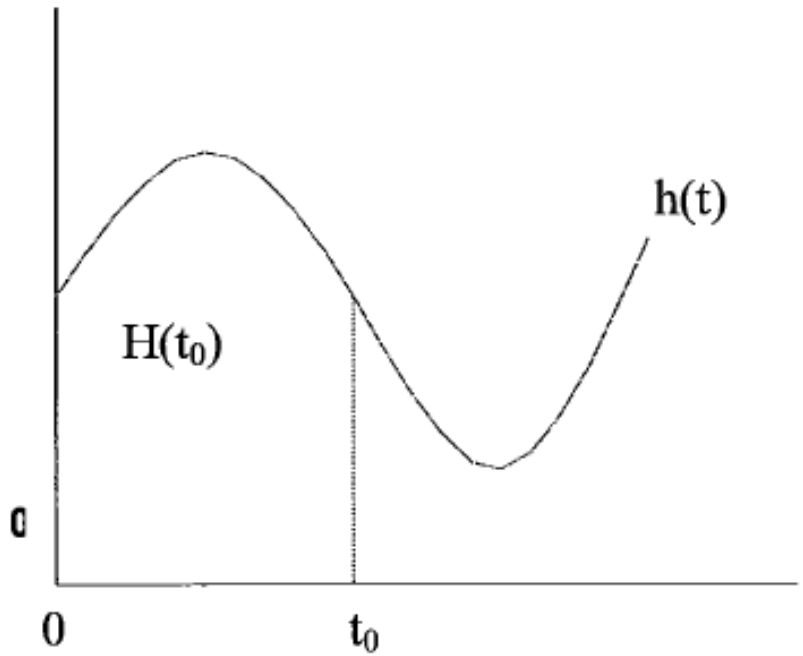
High hazard rate = low survival



Cumulative hazard

- The cumulative hazard function is the area under the curve of the hazard function

$$H(t) = \int_0^t h(s)ds$$



Quantitative relation between survival and hazard function

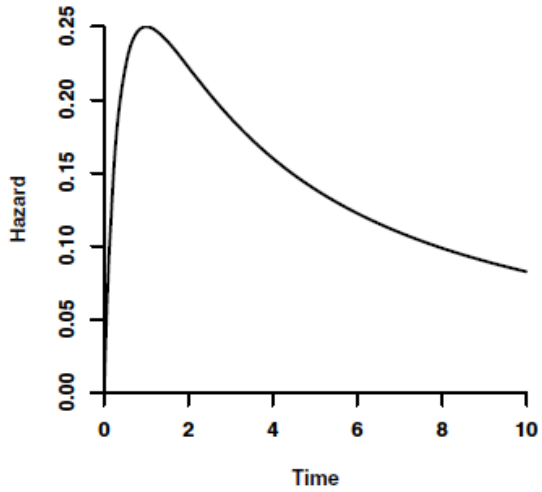
- The survival and hazard function carry the same information and they can be computed from each other

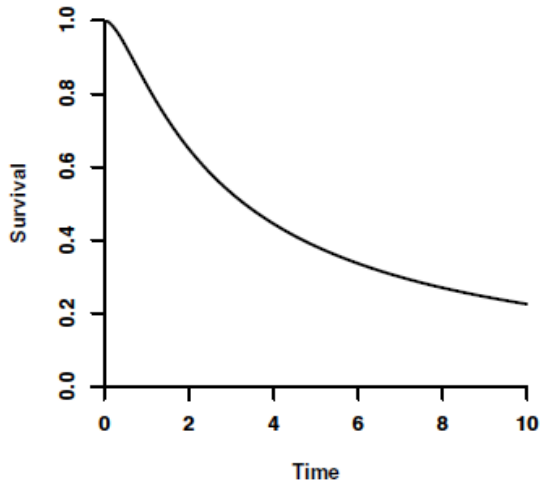
$$h(t) = -\frac{S'(t)}{S(t)}; H(t) = -\log(S(t))$$

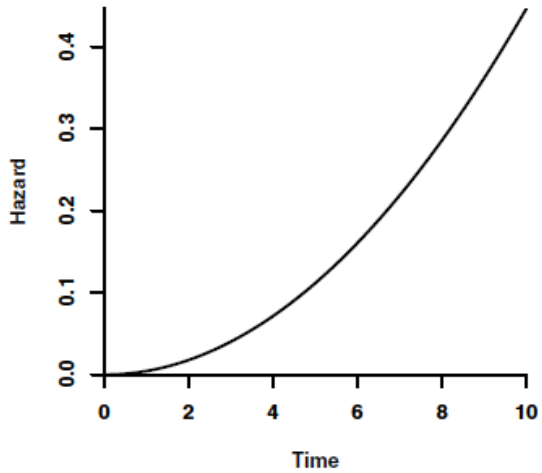
- Inverse relation between survival and hazard

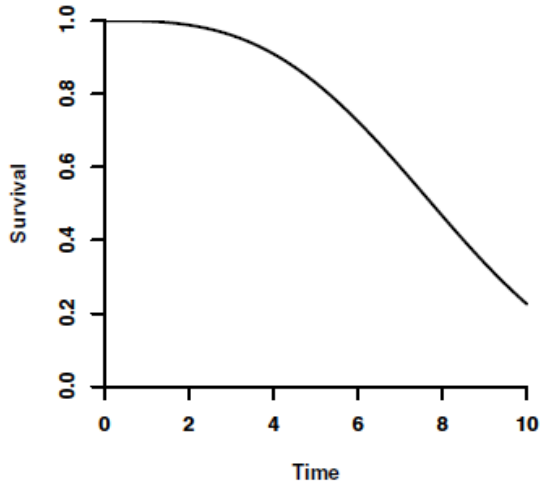
$$S(t) = \exp(-H(t)) = \exp\Big(-\int_0^t h(s)ds\Big)$$

Illustration of the relation





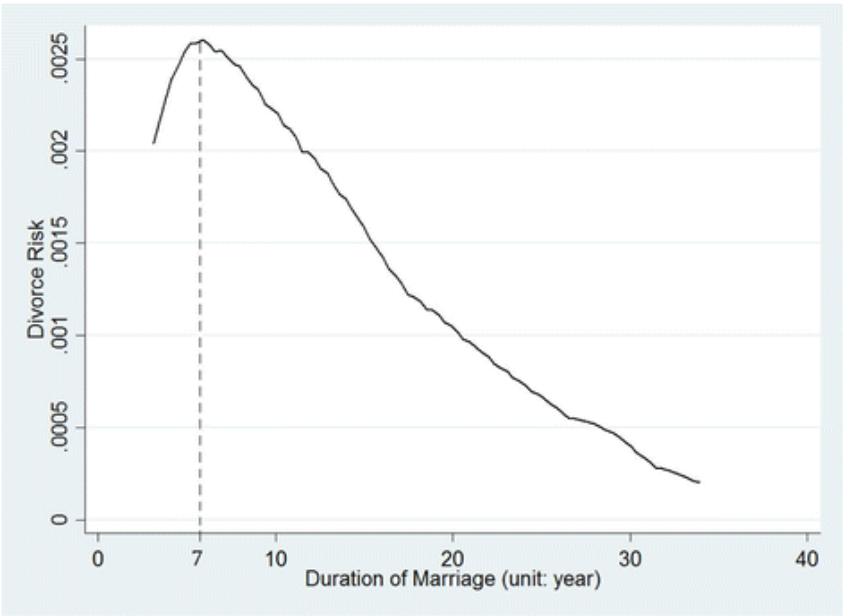




The seven-year itch

Apart from the famous movie with Marilyn Monroe ...

- The seven-year itch refers to the peak of divorce rate after seven years of marriage



Density

- Formally given by

$$f(t) = \lim_{dt \to 0} \frac{P(t \leq \tilde{T} < t + dt)}{dt}$$

- Informally by

$$f(t) \approx P(\tilde{T} = t)$$

- Remember that

$$h(t) \approx \frac{P(\tilde{T} = t)}{P(\tilde{T} \geq t)} = \frac{f(t)}{S(t)}$$

- In other words, we have the relation

$$f(t) = h(t) \cdot S(t)$$

Likelihood

Contribution to likelihood

- Subject i contributes
  - $S(t_i)$, if censored ($d_i = 0$)
  - $f(t_i)$, if event ($d_i = 1$)
- Since $f(t_i) = h(t_i)S(t_i)$, we can write this contribution in one formula as

$$h(t_i)^{d_i} S(t_i)$$

- Likelihood of sample of i independent contributions will be

$$L = \prod_{i=1}^{n} h(t_i)^{d_i} S(t_i)$$

- Becomes especially useful when a *model* for the hazard is employed (such as a proportional hazards model)

Proportional hazards

- The Cox model specifies that the hazard, given covariates x, is given by

$$h(t \mid x) = h_0(t) \exp(\beta^\top x)$$

- β is a p-vector of regression coefficients
- $\exp(\beta_j)$ is the hazard ratio corresponding to covariate x_j
- $h_0(t)$ is an unspecified baseline hazard function
- In a sense, Cox's proportional hazards model models observed heterogeneity
- Subjects may have a different hazard, depending on the specific values of their covariates
- Hazards of subjects with covariates x^* and $\tilde{x}$ are different, except if $\beta^\top x^* = \beta^\top \tilde{x}$

Selection effects of the Cox model

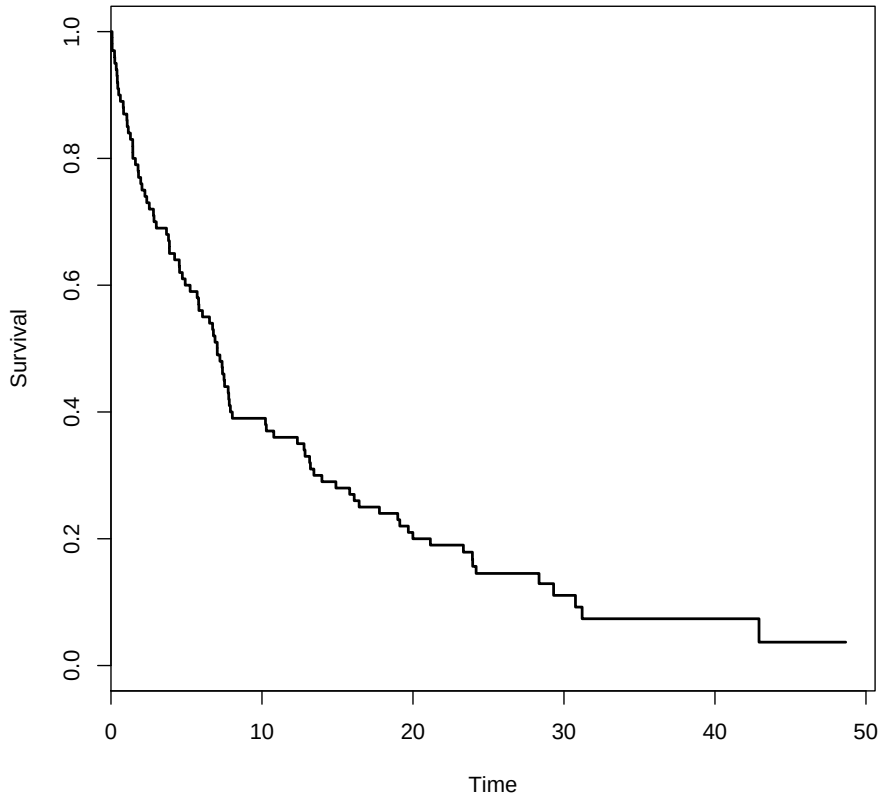
- The Cox model is well known
- We assume some familiarity with the Cox model
- Aim here is to highlight some of the effects of the Cox model on survivors
- For simplicity start with one covariate x
- Let us assume
  - It has a standard normal distribution (mean 0, variance 1)
  - $\beta > 0$
- Two questions for you:
  1. What are mean and variance of X at baseline?
  2. What are mean and variance of X among subjects at risk at $t = 1$?
     - Do you think it will be higher or lower?

Small simulation

- One replication, with sample size $n = 100$
- $X \sim N(0, 1)$, $\beta = 1$
- Baseline exponential with rate 0.1 (mean 10)
- Censoring uniform on $(20, 50)$

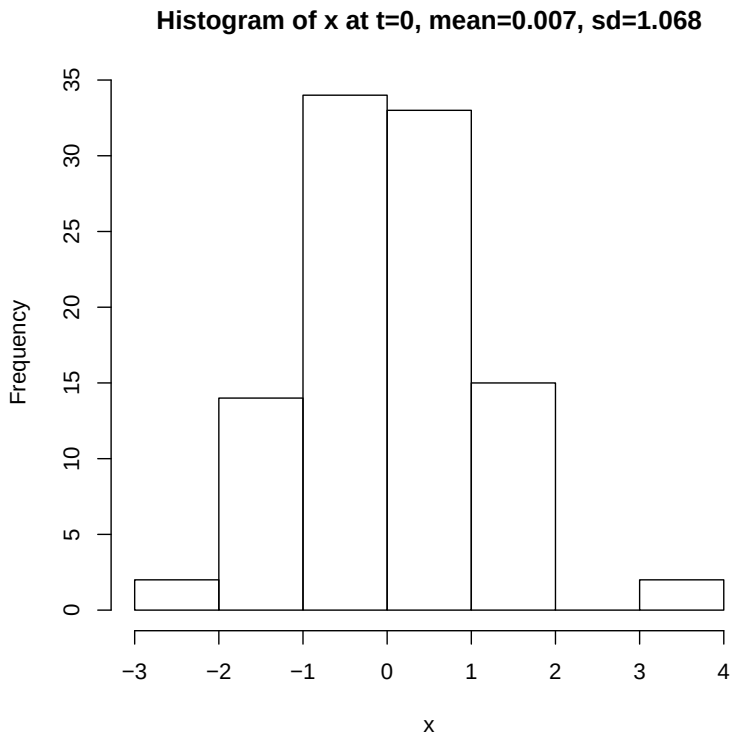
Results

- X had mean -0.007 and SD 1.068
- Estimated β: 0.943 (SE 0.127)
- Estimated overall survival curve

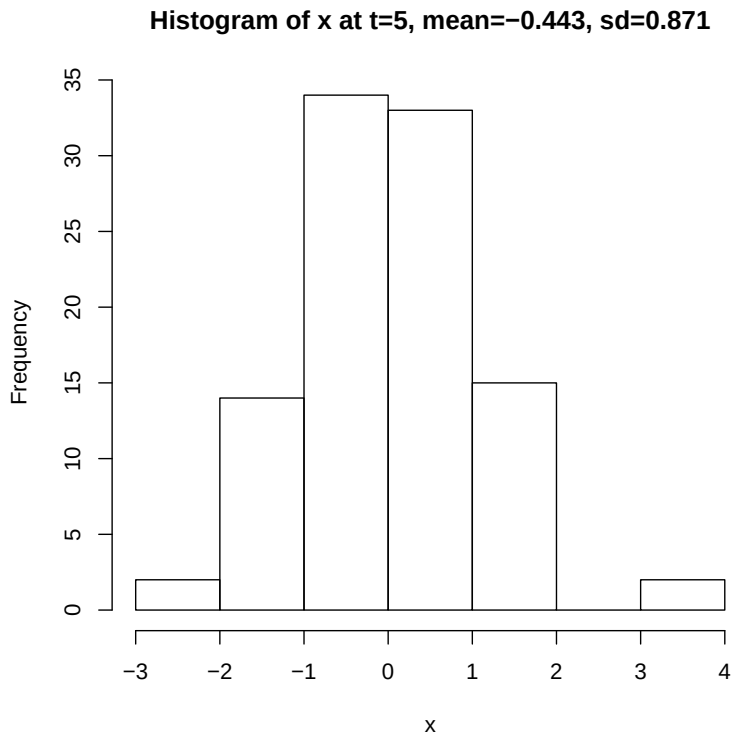


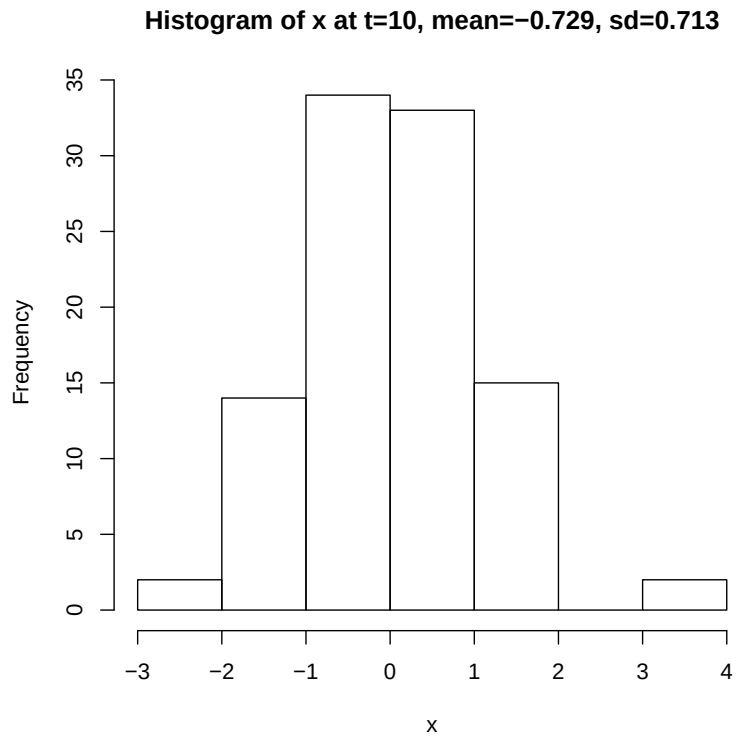
Distribution of X

At baseline



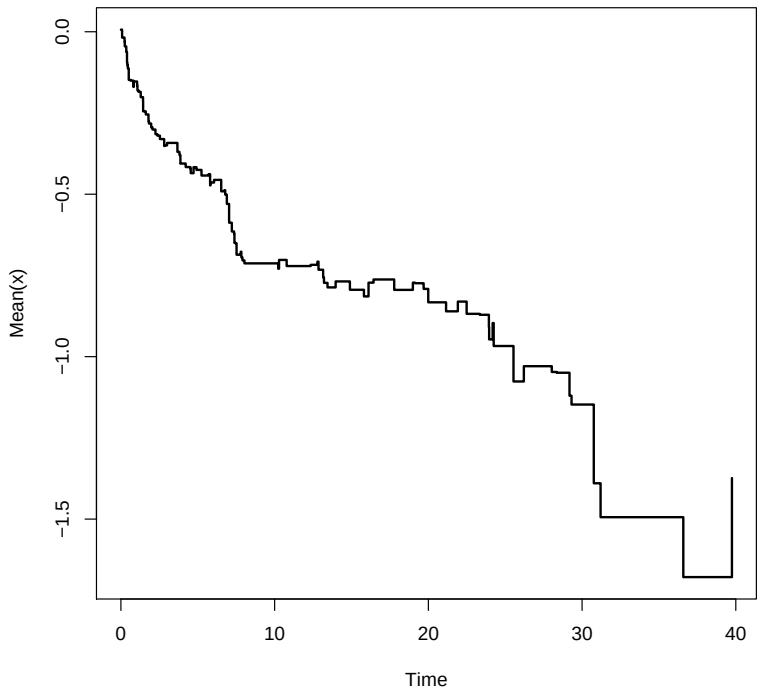
What about the distribution of X later on?

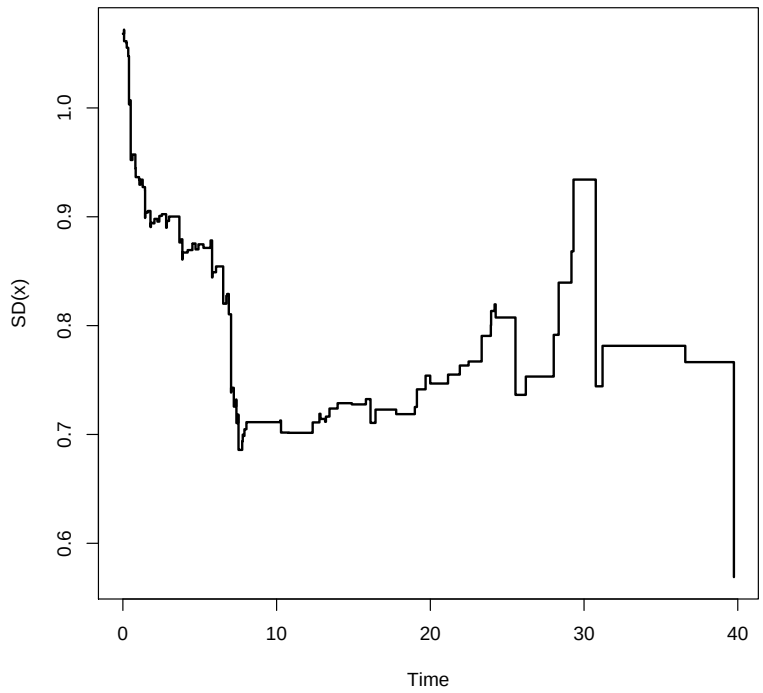




Mean and SD over time

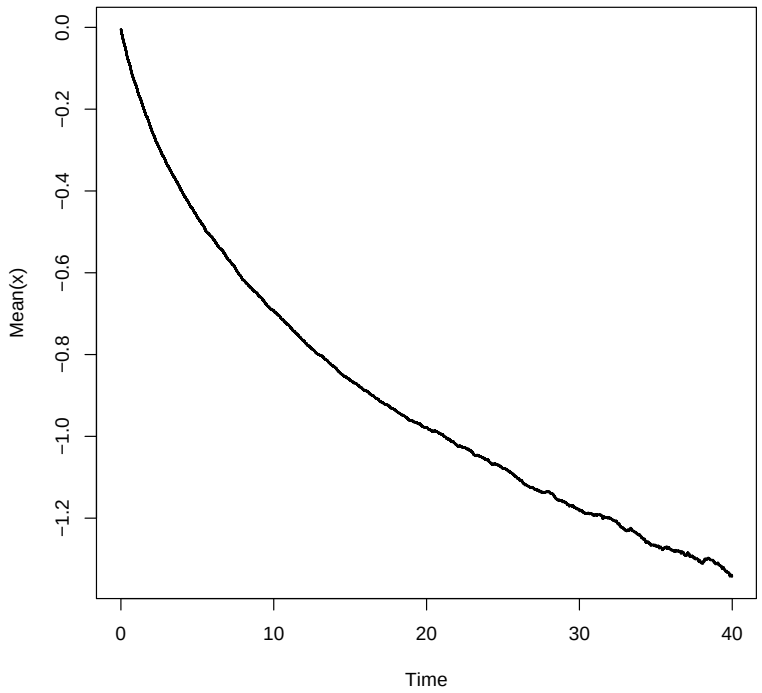
- Mean at time 0, 5, 10: -0.007, -0.443, -0.729
- SD at time 0, 5, 10: 1.068, 0.871, 0.713
- Plots (over time):

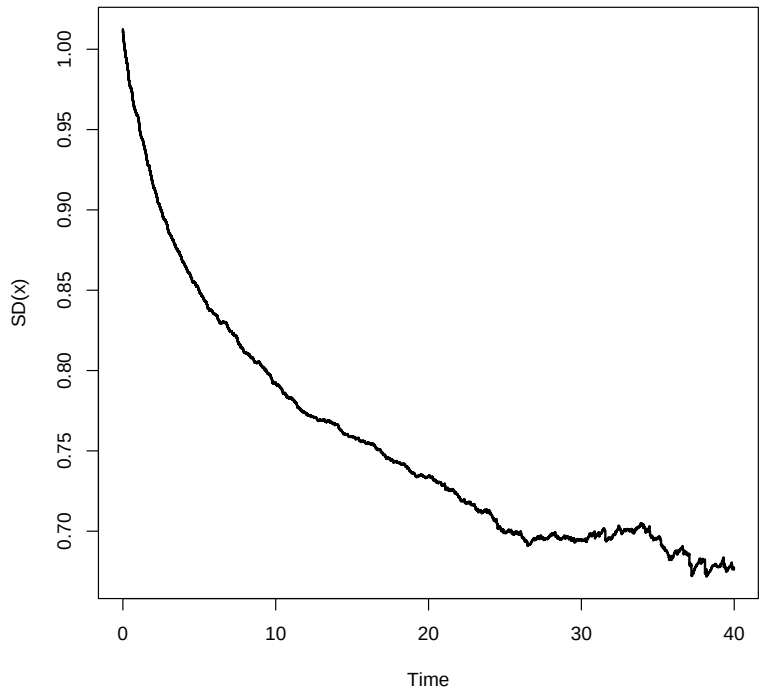




Larger sample size

- Same thing, with $n = 10,000$





Take home message

- If some subjects have higher hazards than others
  - Those with higher hazards die earlier
  - The ones that remain tend to have lower hazards
  - And are more alike
  - With explained heterogeneity, this means that
    1. The means of x of those at risk decreases over time
    2. The variances of x of those at risk decreases over time

The proportional hazards assumption

For simplicity with one covariate x

- Cox's proportional hazards model specifies

$$h(t \mid x) = h_0(t) \exp(\beta x)$$

- The proportional hazards (PH) assumption specifies that the ratio $h(t \mid x^*)$ divided by $h(t \mid \tilde{x})$ equals $\exp(\beta(x^* - \tilde{x}))$ and *does not depend on time*
- The PH assumption is violated if

$$h(t \mid x) = h_0(t) \exp(\beta(t) x)$$

and $\beta(t)$ is not constant

Schoenfeld residuals

- Grambsch & Therneau developed and implemented a very useful way of checking the PH assumption
- Based on scaled *Schoenfeld residuals*
- Schoenfeld residuals are covariate specific
- A smoothed average over time is calculated
- A flat horizontal line means that the PH assumption is fulfilled
- The shape suggests how the effect changes through time
- Formal test associated with Schoenfeld residuals
- Theory beyond scope of this course, just show you some results when applied to simulated data

Omitting covariates causes non-PH

- The following slides are meant to show you what happens when you omit covariates

Simulation

- Single replication, with large sample size $n = 10,000$
- Two independent covariates X_1 and X_2, both $\sim N(0,1)$, $\beta_1 = \beta_2 = 1$
- Baseline exponential with rate 0.1 (mean 10)
- Censoring uniform on $(20, 50)$

Cox with two covariates

```
> c12 <- coxph(Surv(time, status) ~ x1 + x2, data=d)
> c12

## Call:
## coxph(formula = Surv(time, status) ~ x1 + x2, data = d)
##
##       coef exp(coef) se(coef)     z       p
## x1 1.0016    2.7225   0.0138 72.7 <2e-16
## x2 1.0240    2.7843   0.0140 73.2 <2e-16
##
## Likelihood ratio test=9014  on 2 df, p=0
## n= 10000, number of events= 8240
```

- Both estimated regression coefficients very close to 1

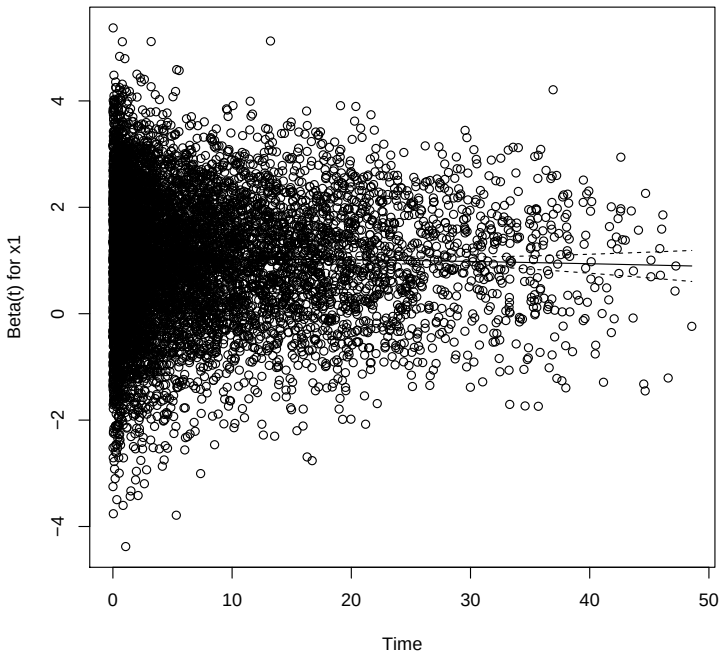
Results of cox.zph

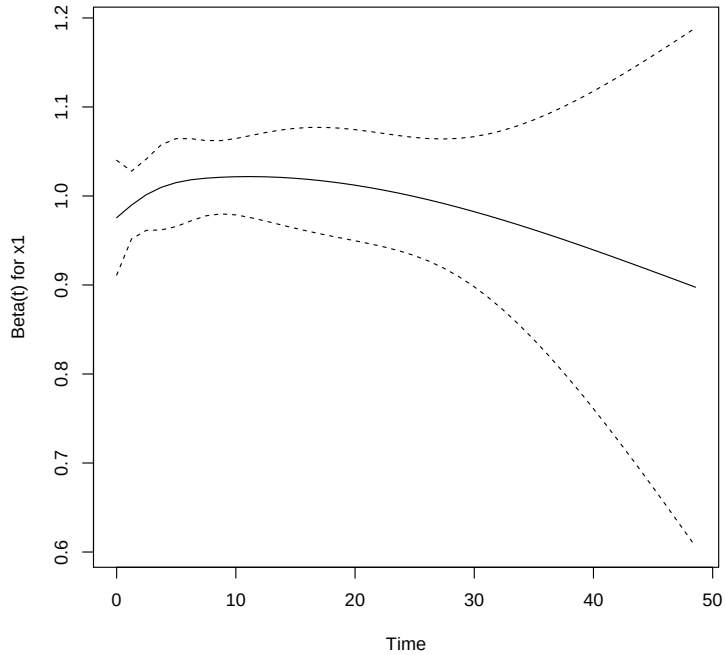
```
> cz12 <- cox.zph(c12, transform="identity")
> cz12

##             rho  chisq     p
## x1      0.00101 0.0081 0.928
## x2     -0.00357 0.1050 0.746
## GLOBAL      NA 0.1510 0.927

> plot(cz12)
```

- Test indicates no departures from PH
- Plots shown on next slide

Plots of cox.zph

- On the left with `resid=TRUE`, on the right with `resid=FALSE`
- Plots for x_2 very similar





Omitting one covariate

- Same dataset, now omitting x_2

```
> c1 <- coxph(Surv(time, status) ~ x1, data=d)
> c1

## Call:
## coxph(formula = Surv(time, status) ~ x1, data = d)
##
##       coef exp(coef) se(coef)    z      p
## x1 0.7028    2.0195   0.0124 56.6 <2e-16
##
## Likelihood ratio test=3271  on 1 df, p=0
## n= 10000, number of events= 8240
```

- Note that the estimated regression coefficient is quite a bit smaller than 1!

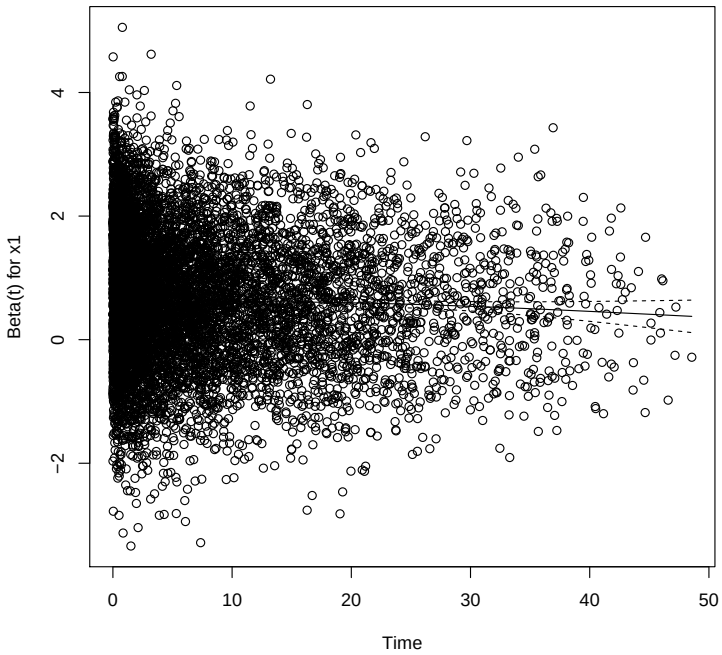
Results of cox.zph

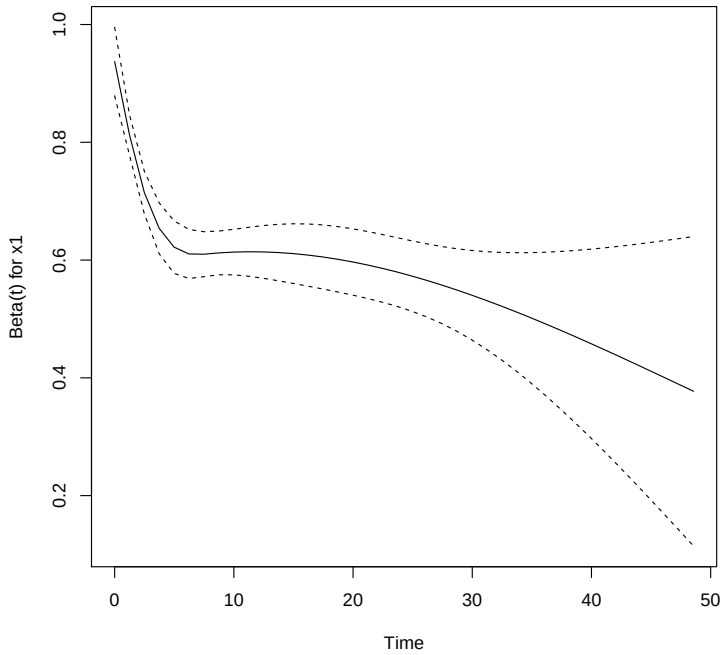
```
> cz1 <- cox.zph(c1, transform="identity")
> cz1

##         rho chisq        p
## x1 -0.0852  55.3 1.06e-13

> plot(cz1)
```

- Test indicates clear departure from PH
- Plots shown on next slide

Plots of cox.zph

- On the left with `resid=TRUE`, on the right with `resid=FALSE`





Take home message 2

- Suppose we have a vector of covariates x
- Suppose a PH model holds for x
- Suppose we can split x into $x = (x_{\text{incl}}, x_{\text{omit}})$ and β into $\beta = (\beta_{\text{incl}}, \beta_{\text{omit}})$
- So the correct model is

$$h(t \mid x) = h_0(t) \exp(\beta_{\text{incl}}^\top x_{\text{incl}} + \beta_{\text{omit}}^\top x_{\text{omit}})$$

- If we fit a PH model using only x_{incl}
- Then
  1. Estimate of β_{incl} will be biased (attenuated towards 0)
  2. The PH assumption for β_{incl} will be violated

Conditional versus marginal

- In the model

$$h(t \mid x) = h_0(t) \exp(\beta_{\text{incl}}^\top x_{\text{incl}} + \beta_{\text{omit}}^\top x_{\text{omit}})$$

  β_{incl} quantifies the effect of x_{incl}, for given values of x_{omit}
- We say that β_{incl} is the conditional effect of x_{incl}, given x_{omit}
- And $h_0(t) \exp(\beta_{\text{incl}}^\top x_{\text{incl}} + \beta_{\text{omit}}^\top x_{\text{omit}})$ is the conditional hazard, given x_{omit}
- What we illustrated is the marginal effect of x_{incl}
- It describes the marginal hazard $h(t \mid x_{\text{incl}})$; we just saw that this marginal hazard was *not* given by $h_0(t) \exp(\beta_{\text{incl}}^\top x_{\text{incl}})$
- The marginal hazard here is still conditional on x_{incl}
  - It describes the hazard given the included covariates
  - At time t, this is obtained by averaging over the distribution of x_{omit}
    - To be precise: the conditional distribution given survival until time t

Unobserved heterogeneity

- We just saw
  1. Selection effects of observed heterogeneity, through observed covariates
  2. Bias and violation of PH, when omitting important covariates
- In reality, we often
  - Cannot measure all covariates that we know or suspect are important (i.e., have an effect on survival)
  - Do not know all covariates that have an effect on survival
  - These covariates are omitted from a proportional hazards model
- This leads to unobserved heterogeneity

Unobserved heterogeneity

- Suppose we have covariates $x = (x_{\text{incl}}, x_{\text{omit}})$
- Only x_{incl} are included into the model, x_{omit} are omitted, because we haven't measured them, we don't know about them or just did not include them into the model
- If the correct model is

$$h(t \mid x) = h_0(t) \exp(\beta_{\text{incl}}^\top x_{\text{incl}} + \beta_{\text{omit}}^\top x_{\text{omit}})$$

- Then we can summarize all these unmeasured or unknown covariates and their effects into a latent, unobserved random variable $U = \beta_{\text{omit}}^\top x_{\text{omit}}$
- So we have

$$h(t \mid x_{\text{incl}}, U) = h_0(t) \exp(\beta_{\text{incl}}^\top x_{\text{incl}} + U) = Z h_0(t) \exp(\beta_{\text{incl}}^\top x_{\text{incl}})$$

- The random variable Z is called a frailty term
- It is assumed to act multiplicatively on the hazard

Randomness

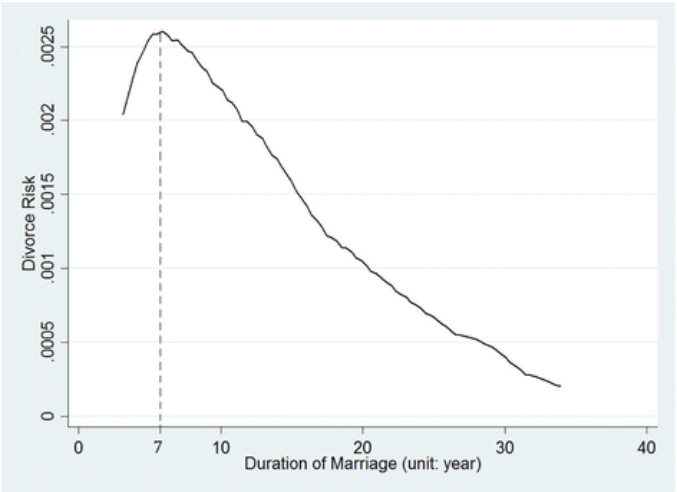
- Additional level of randomness
- Hazard itself describes randomness
- Frailties, random effects, Z, add another level of randomness
- Hard to distinguish one from the other (impossible without any assumptions)

Effects of unobserved heterogeneity

- If we think unobserved heterogeneity to be caused by unmeasured or unknown covariates
- That act multiplicatively on the hazards
- Then we may expect similar effects as we just observed in the Cox model
- Among survivors:
  - Means of decrease over time
  - Variances decrease over time
- Omitting unobserved heterogeneity leads to marginal effects of the included covariates being different from conditional effects
- These and other phenomena will come back in the second lecture
- Odd Aalen calls this “the odd effects of frailty”
  - Which is odd, since his first name is Odd

Conditional versus marginal revisited

- Important to understand distinction
- One is for individual
- Second is for population
- Take the seven-year itch: which hazard is important for *your* marriage?



- Similar issues play a role for covariate effects
- All to be further studied and explained in this course