Survival Data Analysis

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January 2018

Contents

1 Introduction

Summary of models and especially their interpretation (graphically as well as content based) used in Survival Analysis. This document emerged throughout the exam preparation for a lecture on Survival Data Analysis at LMU in winter 2018. Most examples are based on that lecture taught by Prof. Kuechenhoff and Andreas Bender.

2 Big Picture

2.1 Estimation of $S(t)$ and $\lambda(t)$ without Covariate Effects

2.1.1 Non Parametric

- Kaplan-Meier for $S(t)$
- Nelson-Aalen for $\Lambda(t)$
- Breslow for $S(t)$
- Life-table for $\lambda(t)$
- Ramlau-Hansen for $\lambda(t)$

2.1.2 Parametric

- Assume $T_1, ..., T_n \sim$ Distribution(θ) and estimate $\hat{\theta} = argmin_{\theta} l(\theta)$
- **BUT** Censoring
- Random Censoring: $L(\theta) = \prod_{i=1}^{n} \lambda(t_i)^{\delta_i} S(t_i)$

2.2 Regression models with Covariate Effects

2.2.1 Transformation Models

- model $S(t)$ directly
- $log(T) = Y = X^T\beta + \sigma\epsilon$
- Assume $\epsilon \sim$ Distribution(θ)
- Density Transformation: get $F_T(T), f_T(T)$

2.2.2 Semi-Parametric Cox Model

- PH-Assumption: $\frac{\lambda(t|X_1)}{\lambda(t|X_1)} t$
- model $\lambda(t)$ directly
- $\lambda(t|X) = \lambda_0(t) exp(X^T\beta)$
- **parametric** Partial Likelihood Estimation: $PL(\beta) = \prod_{i=1}^{m} \frac{exp(x_i^T\beta)}{\sum_{j \in R(t_i)} exp(x_i^T\beta)}$
- **non-parametric** $\lambda_0(t)$ via Breslow
- **BUT1** effect of β_j assumed to be linear, often is not
- **BUT2** time varying covariates and effects
- **BUT3** time constant baseline hazards

2.2.2.1 Semi-parametric Additive Cox Model (BUT1:)

- $\lambda_(t|X) = \lambda_0(t) exp(f_1(x_1)\beta_1 + ... + f_k(x_k)\beta_k + x_{k+1}\beta_{k+1} + ... + x_p\beta_p)$
- Estimate $f_j(x_j)$ via splines for smooth nonlinear effects

2.2.2.2 Time Varying Covariates and Effects (BUT2:)

2.2.2.2.1 Categorical Covariates

Transform short

i	week	arrested	married	emp1	emp2	emp3
1	2	1	0	1	0	NA
2	3	0	1	1	1	1

to long format:

i	week	arrested	married	emp
1	1	0	0	1
1	2	1	0	0
2	1	0	1	1
2	2	0	1	1
2	3	0	1	1

and fit classic Cox-PH. Equivalent coefficients for both formats **without** covariates because only events in Partial Likelihood.

2.2.2.2.2 Continous Variables

- Create artificial time-dependent variable $\tilde{x}$ and **add** to classic Cox model

- e.g.: age and t:age

2.2.2.2.3 Effects ?

2.3 Extensions of Cox model

Discretisize time in intervals $[a_o, a_1[, ..., [a_{q-1}, a_q[$

2.3.1 Time Discret Survival Models via GLM's

- Transform data in long format with q time-factors
- fit GLM (logistic, cloglog, probit) **wihtout intercept** on event variable as response
- q coefficients β_{0k} for each time interval as some kind of baseline hazard
- **NICE:** GLM Toolbox
- **BUT3:** No hazard/ Survival interpretation, only Odds etc.

2.3.2 Piecewise Exponential Models (BUT3)

- Cox-Model with time varying baseline hazards λ_j for $j = 1, ..., q$
- Transform short

i	t_i	δ_i	x_{i1}	x_{i2}
1	0.25	1	0	3
2	0.13	0	1	5

to long formatted **pseudo-data** :

i	y	a	$log(\Delta)$	x_1	x_2
1	0	0.1	log(0.1)	0	3
1	0	0.2	log(0.1)	0	3
1	1	0.3	log(0.0.5)	0	3
2	0	0.1	log(0.1)	1	5
2	0	0.2	log(0.03)	1	5

- **BUT4:** exploiding parameters for small intervalls and large q
- use **Piecewise Exponential Additive Model**
- **BUT5:** random effects in the data
- use **Piecewise Exponential Additive Mixed Model** with Frailty term
- **BUT6:** only multiplicative effects of the coefficients

2.4 Additive Hazard Regression Models (BUT6)

2.4.1 Aalen Model

- **NICE:** additive effects
- **NICE:** new interpretation graphically
- Idea: model effects of covariates on baseline hazard rate λ_0 **additively**
- Formula: $\lambda(t|X) = \lambda_0(t) + \sum_{k=1}^{p} x_k(t)\beta_k(t) = \lambda_0(t) + x^T(t)\beta(t)$

2.4.2 Cox-Aalen Model

- combine best from both worlds: **additive** effects on $\lambda_0(t)$ that can be influenced by **multiplicative** coefficients
- $\lambda(t|X) = \lambda_0(t) + X(t)\beta(t)exp(Z^T(t)\gamma)$
- $\beta(t)$: time varying additive coefficients
- γ : time constant multiplicative coefficients. Interpretation: multiplicative effect on hazard if rest kept constant.
- **BUT7:** still assumption that $T_i \perp C_i$

2.4.3 Competing Risk Model (But7)

- More than one possible event (e.g.: two types of death) next to censoring of which only one can occur. The events **compete** with each other as only one of them can occur.
- Approaches:

- Seperate "cause-specific" Cox models for each type where the competing events are subsumed in censoring.
  - Problem 1: assumption, that $T_1 \perp T_2$
  - Problem 2: Kaplan-Meier Curves are biased
- Cumulative Incidence Curve as solution to problem 2
- Discretization: Multinomial GLMs

3 Censoring

1. **Right**:
   1. Type 1: study ends before event occured. E.g.: fixed time study of 1 year
   2. Type 2: ...
   3. Type 3: person withdraws from study because of other event. E.g.: interest on cancer death, person is getting shot
2. **Left**: we know when event occurs but we do not know when it started. E.g.: person dies at week 4 on cancer but we don't know the time of the disease outbreak. Our observed survival time of 4 weeks is thus equal (best case) or smaller then the observed.
3. **Left Truncation**: Biased because only people that survived made it to the study. E.g.: deductible in insurances, people with losses < deductibles are not getting observed.

4 Kaplan Meier

4.0.1 Model Equation

Cannot simply $1 - F(t)$ due to censoring. KM takes that into account.

Estimate the **Survival rate** non-parametrically without any covariables:

$$\hat{S}(t) = \prod_{t_k \leq t} (1 - d_k/n_k), \forall t \geq t_1$$

where d_k = number of events at time point t_k (neither dead nor censored) and $n_k = $ amount of people under risk right before time t_k.

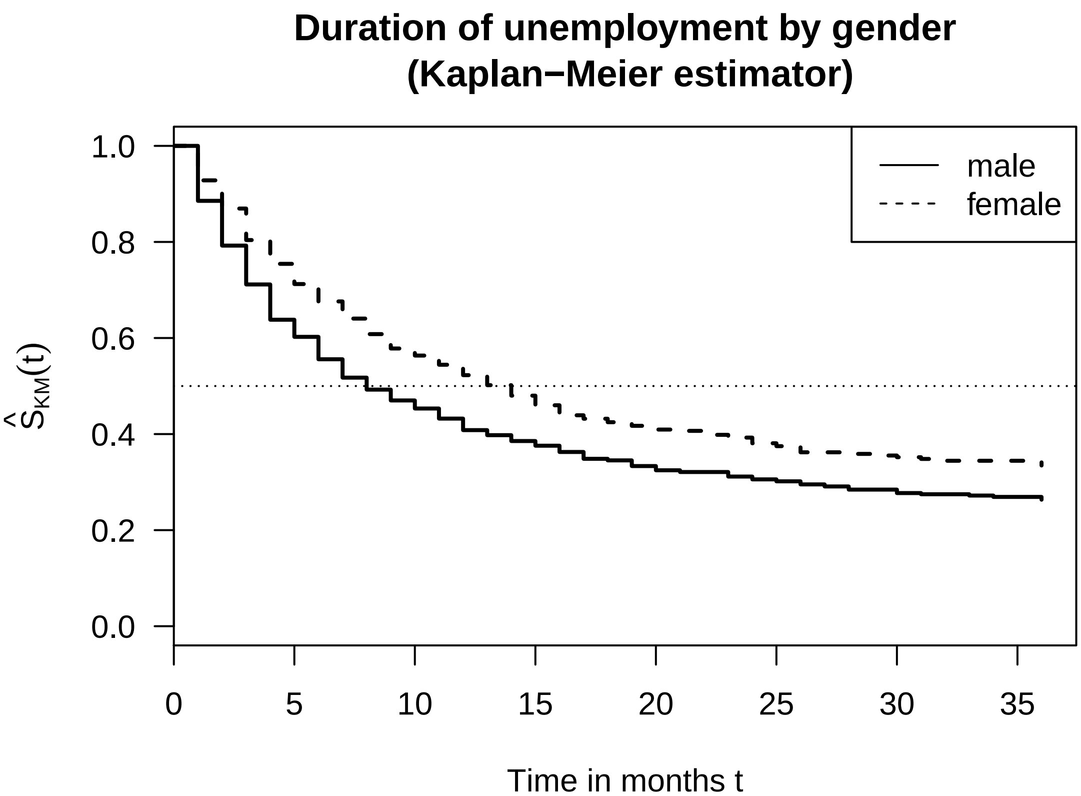
Reveals a step function with jumps at each t_k where events took place.

4.0.2 Data

This is some random SOEP data and we estimate Survival functions for both genders:

```
##   dauer status beginn.monat female male alter bild
## 1    11      0          114      0    1    47    1
## 2    30      1           83      0    1    38    2
## 3     1      1           83      0    1    44    2
## 4    36      0           85      0    1    28    2
## 5     1      1          111      0    1    38    2
## 6     7      0          104      1    0    30    1
```

4.0.3 Model



This gives incidence for the Proportional Hazards assumption as survival curves are more or less parallel.

4.0.4 Test

Plotting estimated confidence intervals **DOES NOT ENABLE** us to interpret signifiance. KI's can cross, and still there is a significant effect.

- Only interpret the p-value of the log rank test!
- log rank test resembles the score test in the cox model.
- '`surfdiff()` for p = 2 > 1 variables: H0: no differencies across 4 resulting groups. If $p < \alpha$: reject H0.

```
## Call:
## survdiff(formula = Surv(dauer, status) ~ female, data = soep)
##
##             N Observed Expected (O-E)^2/E (O-E)^2/V
## female=0 1206      726      651      8.62      22.1
## female=1  794      396      471     11.92      22.1
##
##  Chisq= 22.1  on 1 degrees of freedom, p= 2.6e-06
```

5 Nelson Aalen

6 Accelerated Failure Time Transformation models

6.1 General

Assumptions: 1. covariates have a multiplicative effect on the **Survival time**. E.g.: Survival time for smokers is an accelerated version of the survival time for non-smokers.
2. the survival time follows an assumed distribution that we get applying a density transformation

We model the survival time directly with the log-trafo:

$$log(T) = Y = \beta_0 + X^T\beta + \sigma\epsilon$$

$$T = exp(Y) = exp(\beta_0) * exp(X^T\beta) * exp(\sigma\epsilon)$$

with $\epsilon \sim$ Distribution e.g.: SEV, Normal, logistic, ...

Thus, the effect of the estimated coefficient $\hat{\beta}_j$ on Survival time T is $exp(\beta_j)$

Steps for the estimation: 1. calculate density for T 2. classic Maximum Likelihood Estimation

The exponential and the weibull AFT can be compared with a Cox PH model as they also have proportional (time independent) hazard ratios. This means that the following re-parametrization holds:

$$\beta_{PH} = -\frac{\beta_{\text{AFT: WB or Exp}}}{\sigma}$$

where *sigma* is our scale parameter from the AFT model equation. **This interpretation goes only from AFT to CoxPH, not in both directions!**.

Therefore we compare with this baseline Cox model:

```
## Call:
## coxph(formula = Surv(futime, fustat) ~ ecog.ps + rx, data = ovarian)
##
##   n= 26, number of events= 12
##
##             coef exp(coef) se(coef)      z Pr(>|z|)
## ecog.ps  0.3698    1.4474   0.5869  0.630    0.529
## rx      -0.5782    0.5609   0.5878 -0.984    0.325
##
##         exp(coef) exp(-coef) lower .95 upper .95
## ecog.ps    1.4474     0.6909    0.4582     4.573
## rx         0.5609     1.7829    0.1772     1.775
##
## Concordance= 0.622  (se = 0.088 )
## Rsquare= 0.054   (max possible= 0.932 )
## Likelihood ratio test= 1.45  on 2 df,   p=0.4833
## Wald test            = 1.43  on 2 df,   p=0.4897
## Score (logrank) test = 1.46  on 2 df,   p=0.4808
```

6.2 Exponential

```
##
## Call:
## survreg(formula = Surv(futime, fustat) ~ ecog.ps + rx, data = ovarian,
##     dist = "exponential")
##              Value Std. Error      z        p
## (Intercept)  6.962      1.322  5.267 1.39e-07
## ecog.ps     -0.433      0.587 -0.738 4.61e-01
## rx           0.582      0.587  0.991 3.22e-01
##
## Scale fixed at 1
##
## Exponential distribution
## Loglik(model)= -97.2   Loglik(intercept only)= -98
##  Chisq= 1.67 on 2 degrees of freedom, p= 0.43
## Number of Newton-Raphson Iterations: 4
## n= 26
```

6.2.1 AFT interpretation:

- Geometric mean of survival time: 1055
- 1 unit change in ecog.ps shortens survival time by exp(-0.433) = 0.65
- 1 unit change in rx increases survival time by exp(0.582) = 1.79
- though, both effects are non significant

```
##  (Intercept)      ecog.ps           rx
## 1055.5715021    0.6484732    1.7887244
```

6.2.2 PH interpretation (invert the coefficients)

- 1 unit change in ecog.ps increases the hazard h(t) by 1/exp(0.433) = 1.54
- 1 unit change in rx decreases h(t) by 0.56

```
##  (Intercept)      ecog.ps           rx
## 0.0009473541 1.5420838523 0.5590576235
```

6.3 Weibull

$$T = exp(Y) = exp(X^T\beta)exp(\sigma\epsilon), \text{ with } \epsilon \sim SEV$$

using the **density transformation rule**

$$f_T(T) = f_\epsilon(g^{-1}(T))det|\frac{\partial g^{-1}(T)}{\partial T}|$$

we can show that $T \sim Weibull(\alpha, \lambda)$ with $\alpha = \frac{1}{\sigma}$ and $\lambda = exp(-X^T\beta)$. Thus:

- $\lambda(t|X) = \frac{1}{\sigma}t^{\frac{1}{\sigma}-1}exp(X^T\beta)$

- $S(t|X) = exp(-exp(-X^T\beta)^{\frac{1}{\sigma}} t^{\frac{1}{\sigma}})$

```
##
## Call:
## survreg(formula = Surv(futime, fustat) ~ ecog.ps + rx, data = ovarian,
##     dist = "weibull")
##              Value Std. Error      z        p
## (Intercept)  6.897      1.178  5.857 4.72e-09
## ecog.ps     -0.385      0.527 -0.731 4.65e-01
## rx           0.529      0.529  0.999 3.18e-01
## Log(scale)  -0.123      0.252 -0.489 6.25e-01
##
## Scale= 0.884
##
## Weibull distribution
## Loglik(model)= -97.1   Loglik(intercept only)= -98
##  Chisq= 1.74 on 2 degrees of freedom, p= 0.42
## Number of Newton-Raphson Iterations: 5
## n= 26
```

6.3.1 AFT interpretation:

- Geometric mean of survival time: 988
- 1 unit change in ecog.ps shortens survival time by exp(-0.385) = 0.68

- 1 unit change in rx increases survival time by exp(0.529) = 1.70
- though, both effects are non significant

- If scale parameter `{R, echo = FALSE} survregWB$scale` was close to 1 we would yield an exponential model. Our shape parameter is 1 / scale
- coefficients: `{R, echo = FALSE} exp(coef(survregWB))`

6.3.2 PH interpretation (multiply by -1 and the shape parameter before exp())

- 1 unit change in ecog.ps increases the hazard h(t) by 1.55
- 1 unit change in rx decreases h(t) by 0.55

```
##  (Intercept)      ecog.ps           rx
## 0.0004085855 1.5459383069 0.5498547398
```

6.4 Log Normal

Only AFT Interpretation!

- 1 unit incrase in ecog.ps shortens survival time by exp(-.229) = 0.79
- 1 unit incrase in rx increases survival time by exp(0.813) = 2.25
- Can we interpret the scale parameter? Yes, but how?
- MORE TO ADD! DISCUSS

```
##
## Call:
## survreg(formula = Surv(futime, fustat) ~ ecog.ps + rx, data = ovarian,
##     dist = "lognormal")
##              Value Std. Error      z        p
```

```
## (Intercept)  5.878      1.094  5.373 7.72e-08
## ecog.ps     -0.229      0.537 -0.427 6.70e-01
## rx           0.813      0.537  1.514 1.30e-01
## Log(scale)   0.167      0.228  0.731 4.65e-01
##
## Scale= 1.18
##
## Log Normal distribution
## Loglik(model)= -95.9   Loglik(intercept only)= -97.1
##  Chisq= 2.35 on 2 degrees of freedom, p= 0.31
## Number of Newton-Raphson Iterations: 3
## n= 26
```

6.5 Log logistic

```
##
## Call:
## survreg(formula = Surv(futime, fustat) ~ ecog.ps + rx, data = ovarian,
##     dist = "loglogistic")
##              Value Std. Error      z        p
## (Intercept)  6.161      1.134  5.435 5.49e-08
## ecog.ps     -0.336      0.537 -0.626 5.32e-01
## rx           0.705      0.539  1.308 1.91e-01
## Log(scale)  -0.363      0.248 -1.466 1.43e-01
##
## Scale= 0.695
##
## Log logistic distribution
## Loglik(model)= -96.3   Loglik(intercept only)= -97.4
##  Chisq= 2.07 on 2 degrees of freedom, p= 0.36
## Number of Newton-Raphson Iterations: 4
## n= 26
```

7 Cox Regression model

Estimates coefficents β that have multiplicative effect on time-dependent hazard $\lambda_0(t)$. The baseline hazard is estimated non-parametrically via Breslow estimate. Thus, we yield step-functions for visualization, estimation, …

super sweet R-bloggers post on Cox models

7.0.1 Model equation

$$\lambda_i(t) = \lambda_0(t) exp(x_i'\beta)$$

To get the estimator for the cumulative Hazard and the Survival rate:

1. estimate βs via Cox **parametrically**

2. estimate non-parametrically baseline hazards $\lambda_0(t)$ e.g. via Breslow **non-parametrically**

3. calculate for each t $\lambda(t) = \lambda_0(t) exp(x_i' \beta)$

4. cumulate the $\lambda(t)$ to the cumulative Hazards $\Lambda_t = \sum_{i=1}^{t} \lambda_i$. `basehaz()` plottet Λ_0

5. calculate estimated Survival $S(t) = exp(-\Lambda_t)$
   Therfore Cox PH model is termed **semi parametric**.

7.0.2 Data

where delta depicts the event indicator (delta = 1: non-censored, delta = 0: censored)

```
##   type time delta
## 1    1    1     1
## 2    1    3     1
## 3    1    3     1
## 4    1    4     1
## 5    1   10     1
## 6    1   13     1
```

7.0.3 Model

We are searching for the effect of the binary treatment type.

- Person with type 2 has a multiplicative factor exp(0.4664) = 1.594245 higher hazard rate than a person with type 1 (ceteris paribus in case of other covariates)

- this effect is not significant as the H0 can not be rejected at $\alpha = 0.05$, REMIND but this does not imply testing of the PH assumption

- (log rank-) score test: tests for significant differencies in the survival curves for the two subpopulations seperated by the **categorical variable** of interest (here: treatment). This means that the probability of an event occurring at any time point is the same for each subpopulation. H0: they do not differ -> p > 0.05: H0 cannot be rejected -> no significant effect of treatment. If there are more than 1 categorical variablewe have the H0: no effect of no covariate at all. Reject again if $p < \alpha$
- ‘`surfdiff()` for p = 2 > 1 variables: H0: no differencies across 4 resulting groups. If $p < \alpha$: reject H0.

- Partial likelihood test: for **continuos** variables! WHAT HAPPENS WITH MORE COVARIATES? E.G.: one significant, the other not

Summary of the Cox-PH model:

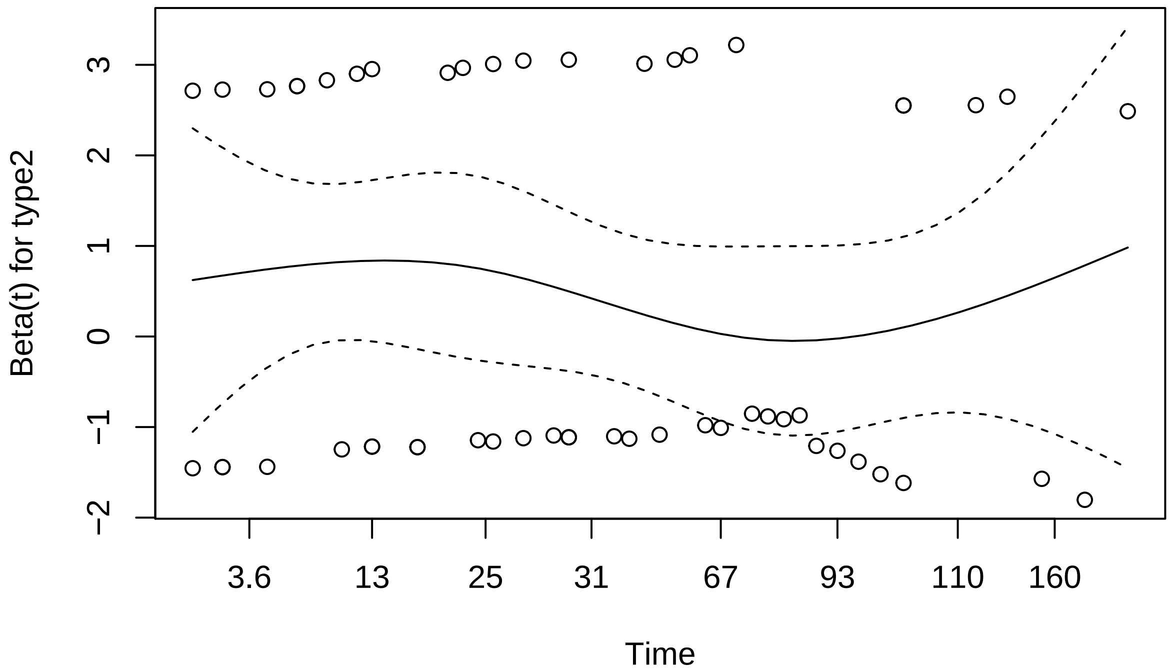
```
## Call:
## coxph(formula = Surv(time, delta) ~ type, data = tongue)
##
##   n= 80, number of events= 53
##
##          coef exp(coef) se(coef)     z Pr(>|z|)
## type2 0.4664    1.5942   0.2804 1.663   0.0963 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##       exp(coef) exp(-coef) lower .95 upper .95
## type2     1.594     0.6273    0.9201     2.762
##
## Concordance= 0.564  (se = 0.036 )
```

```
## Rsquare= 0.033   (max possible= 0.993 )
## Likelihood ratio test= 2.67  on 1 df,   p=0.102
## Wald test            = 2.77  on 1 df,   p=0.09632
## Score (logrank) test = 2.81  on 1 df,   p=0.09343
```

7.0.4 Test the Cox PH assumption for the covariates

7.0.4.1 Graphically

The scaled Schoenfeld residuals are used for that test and plotted against the time. Do this for each covariate to check the PH assumption for each covariate. If they **randomly and unstructured** center around zero: PH assumption holds! If not, not. The plot estimates a smooth function of the residuals over time for better visualization. Holds here:

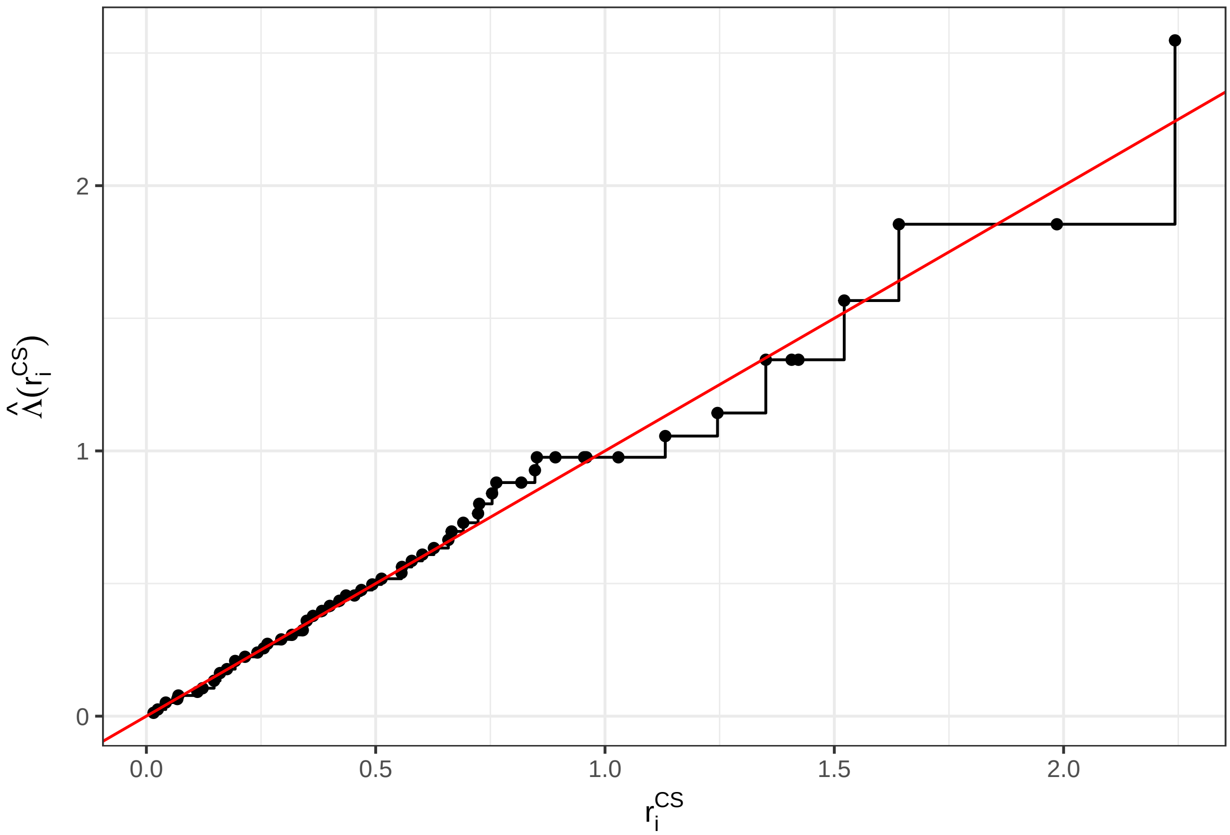


7.0.4.2 Test PH

Also based on Schoenfeld residuals, not exam-relevant. If $p >> 0.05$ there is no violation of the PH.

7.0.5 Test overall fit

Plot Cox-Snell residuals vs. Cumulated Hazard. If they share the diagonal, everything is fine and we have a good overall model fit.

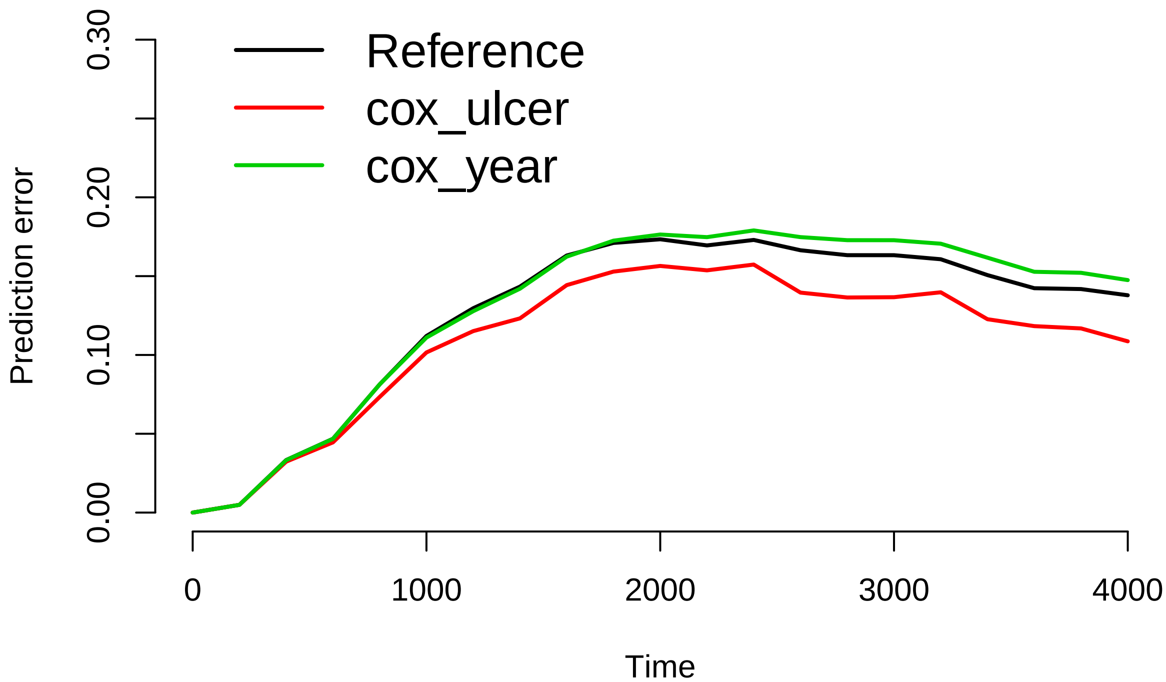


8 Model fit Analysis

8.1 Prediction Error Curves (PEC)

The predicted survival time for each time point is compared with the true survival time within the **Brier Score**. Some magic is added such as *inverse probability of censoring weights (IPCW)* to account for right censoring. Then scores for each time point are computed using Cross-Validation and the Brier Scores over time are plotted for all desired models. The lower the score, the better. This method is **model agnostic**.

For Melanoma compare predictive performance of Cox model with only variable ulcer as predictor with the reference Kaplan-Meier estimates and a Cox-PH model that uses year as a linear predictor. We see, that our cox-model outperforms the simple Kaplan-Meier estimator (which does not use any variables) and both outperform the stupid Cox model with time as linear predictor.



8.2 Residuals

- Schoenfeld
- Martingale
- Deviance
- Cox-Snell

8.2.1 Schoenfeld Residuals

Use case: test PH assumption for each covariate

Idea: compute Schoenfeld residuals for Variable k and m observations. Those residuals should be independent of the survival time. This is the test that `cox.zph()` performs.

PH: effects of covariates are proportional and thus, time invariant. Thus, check for timely structure in residuals, if some timely structure *is left in the residuals*, the models assumption failed.

8.2.1.1 Test

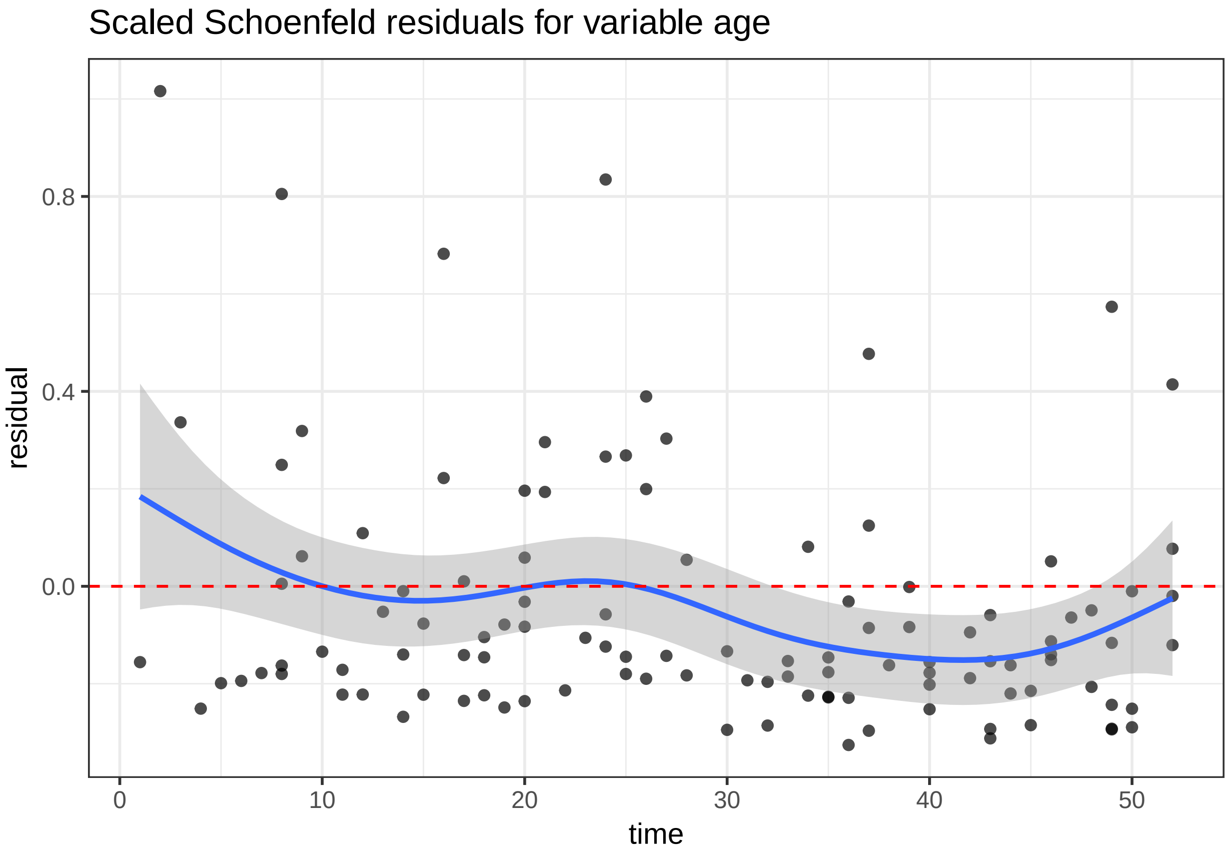
```
##                   rho  chisq       p
## fin            0.0267 0.0838 0.77227
## age           -0.2264 7.5618 0.00596
## prio          -0.0657 0.5330 0.46533
## mar            0.1327 2.1143 0.14593
## employed.lag1 -0.0427 0.2066 0.64942
## GLOBAL             NA 9.4135 0.09366
```

Small p-value for variable age indicates problem with the PH assumption here. High value for employed.lag1 indicates nice fulfillment of PH assumption.

Can we observe this graphically?

8.2.1.2 Graphically

Plot the Schoenfeld residuals for variable age:

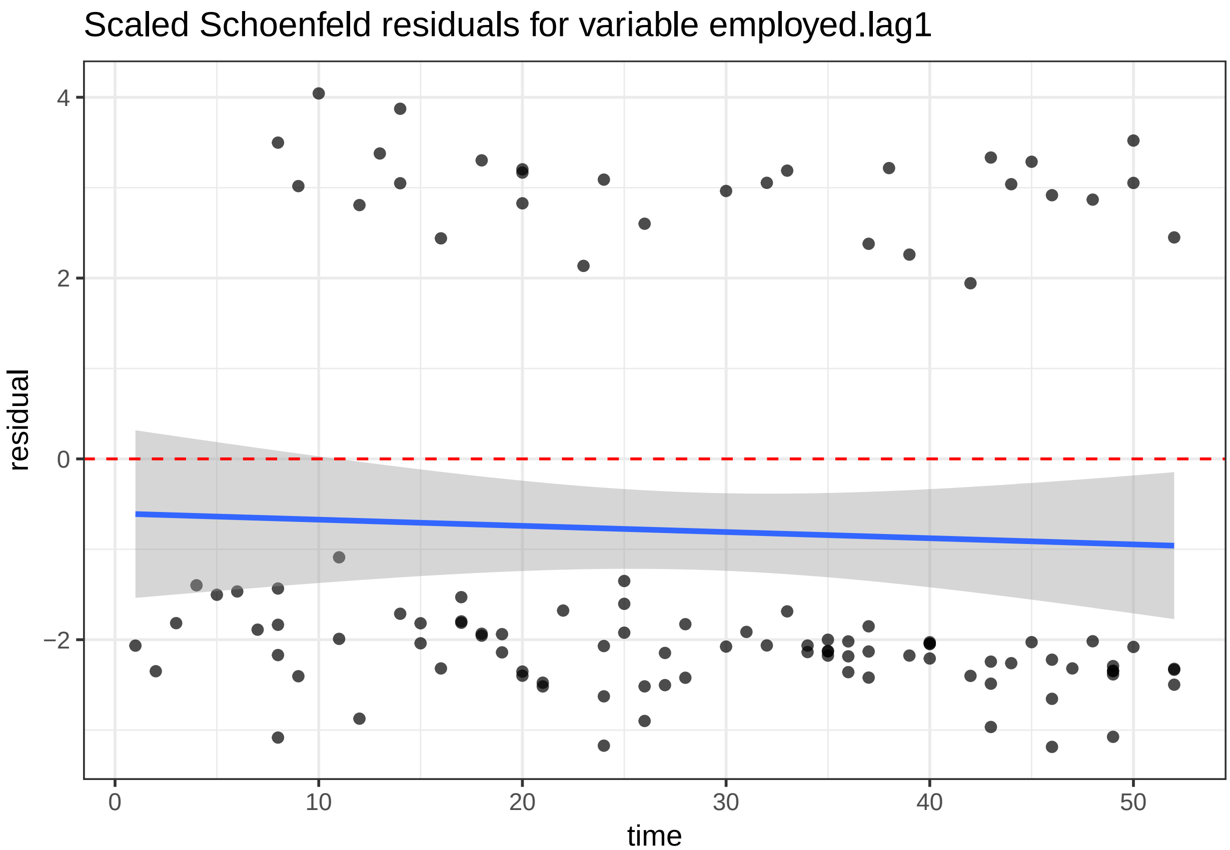


PH assumption violated because there is non linear structure in the data.

What can we do?

1. Exclude variable
2. **additionally** model time varying effect as e.g. $x_{age} \cdot log(1 + t)$
3. non-linearly e.g. using splines

Check variable `employed lag1` that had huge p-value in zph test (good sign for PH):



We see what we expected: there seems to be no PH violation. Sweet!

8.2.2 Cox Snell residuals

Use case: Check overall goodness of fit

8.2.2.1 Graphically

H0: Model works - Cox-snell residuals should follow an Exp(1) distribution. If the cox-snell-residuals distribution deviates strongly from the Exp(1), the model does not fit well.

8.2.2.2 Test

8.2.2.3 Model

8.2.2.4 Example

Check the overall goodness of fit for a simple cox model:

```
## Call:
## coxph(formula = Surv(time, delta) ~ type, data = tongue)
##
##   n= 80, number of events= 53
##
##          coef exp(coef) se(coef)     z Pr(>|z|)
```

```
## type2 0.4664    1.5942   0.2804 1.663   0.0963 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##       exp(coef) exp(-coef) lower .95 upper .95
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```
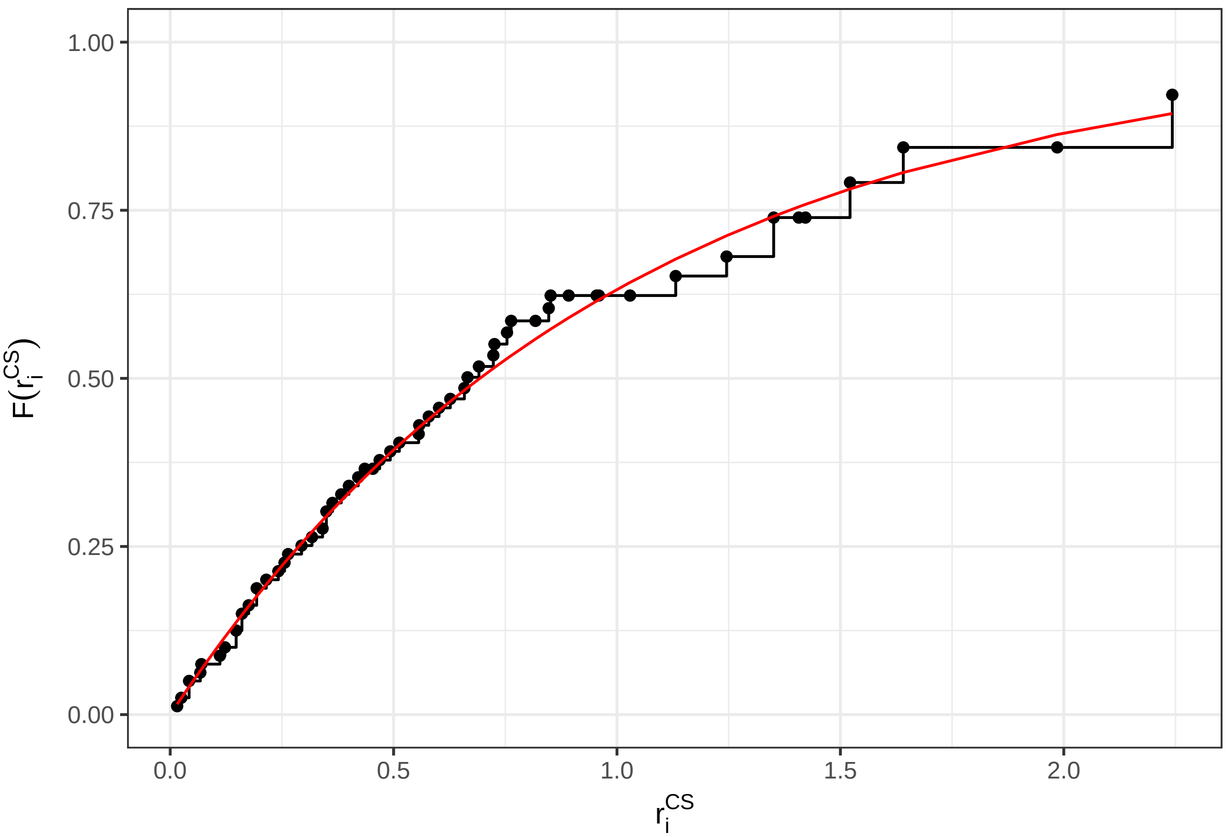
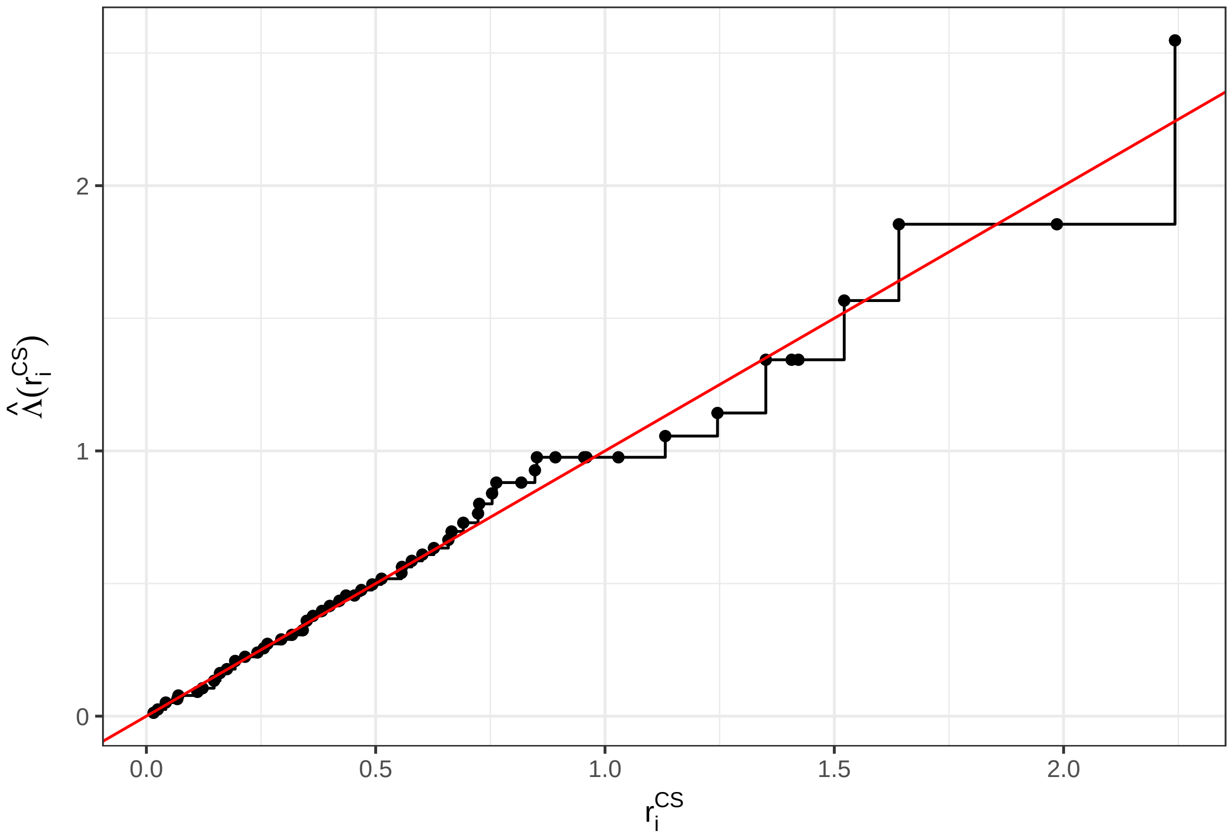





Two options: 1. Plot cs-residuals against estimated distribution Function values. Their distribution should then follow a standard exponential distribution if the model is fit correctly. 2. Plot against estimted cumulative hazard function. This should result in a straight line if the model fits the data.

8.3 (Partial) Log Likelihood Ratio Test

Idea: Test reduced model β_0 against full model β and check, which fits better.

Formally: $H0 : C\beta = d$ and $H1 : C\beta \neq d$.

In standard R output: reduced model is model with all $\beta_0^T = 0^T$ and the full model is the fitted model. Formally this means $H0 : C\beta = 0$ and $H1 : C\beta \neq 0$.

Test statistics:

$$lq = 2(logPL(\hat{\beta}) - logPL_{H0}(\hat{\beta})) \sim \chi^2_{df}$$

H0: all coefficients are insignificant.

- $lq > \chi^2_{df}(1-\alpha) \rightarrow$ reject H0
- $p < \alpha \rightarrow$ reject H0 aka $\hat{\beta}$ **is not insignificant**.

Example:

```
## Call:
## coxph(formula = Surv(time, delta) ~ type, data = tongue)
##
##   n= 80, number of events= 53
##
##          coef exp(coef) se(coef)     z Pr(>|z|)
```

```
## type2 0.4664    1.5942   0.2804 1.663   0.0963 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##       exp(coef) exp(-coef) lower .95 upper .95
## type2     1.594     0.6273    0.9201     2.762
##
## Concordance= 0.564  (se = 0.036 )
## Rsquare= 0.033   (max possible= 0.993 )
## Likelihood ratio test= 2.67  on 1 df,   p=0.102
## Wald test            = 2.77  on 1 df,   p=0.09632
## Score (logrank) test = 2.81  on 1 df,   p=0.09343
```

The p-value of the Likelihood ratio test is $0.102 > \alpha = 0.05$: we cannot reject the H0 that the coefficient vector β (here with only one coefficient for `type2`) is equal to 0. This goes in line with the p-value for this coefficient. We have 1df as there is only one coefficient to be tested. Works the same way with additional coefficients.

8.4 (Log rank) Score test

Idea: Tests for significant differencies in the survival curves for the two subpopulations seperated by the **categorical variable** of interest (above: type2). This means that the probability of an event occurring at any time point is the same for each subpopulation.

- H0: they do not differ
- p > 0.05: H0 cannot be rejected -> no significant effect of type2.
- If there are more than 1 categorical variable we yield the H0: no effect of no covariate at all. Reject H0 again in favor of significant effects if $p < \alpha$.

9 Semi-parametric additive Cox model

- $\lambda_(t|X) = \lambda_0(t)exp(f_1(x_1)\beta_1 + ... + f_k(x_k)\beta_k + x_{k+1}\beta_{k+1} + ... + x_p\beta_p)$
- Estimate $f_j(x_j)$ via splines for smooth nonlinear effects
- Example: age has non-linear effect, smooth age variable via Splines

10 Cox model: time varying covariates

10.1 Continous covariates

10.2 Categorical covariates

We convert

```
##   week arrest fin age race wexp mar paro prio educ emp1 emp2 emp3 emp4
## 1   20      1   0  27    1    0   0    1    3    3    0    0    0    0
## 2   17      1   0  18    1    0   0    1    8    4    0    0    0    0
## 3   25      1   0  19    0    1   0    1   13    3    0    0    0    0
## 4   52      0   1  23    1    1   1    1    1    5    0    0    0    0
##   emp5 emp6 emp7 emp8 emp9 emp10 emp11 emp12 emp13 emp14 emp15 emp16 emp17
## 1    0    0    0    0    0     0     0     0     0     0     0     0     0
## 2    0    0    0    0    0     1     1     1     1     1     0     0     0
```

```
## 3    0    0    0    0    0     0     0     0     0     0     0     0     1
## 4    1    1    1    1    1     1     1     1     1     1     1     1     1
##   emp18 emp19 emp20 emp21 emp22 emp23 emp24 emp25 emp26 emp27 emp28 emp29
## 1     0     0     0    NA    NA    NA    NA    NA    NA    NA    NA    NA
## 2    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA
## 3     0     0     0     0     0     0     0     0    NA    NA    NA    NA
## 4     1     1     1     1     0     0     0     0     0     0     0     0
##   emp30 emp31 emp32 emp33 emp34 emp35 emp36 emp37 emp38 emp39 emp40 emp41
## 1    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA
## 2    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA
## 3    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA
## 4     0     0     1     1     1     1     1     1     1     1     1     1
##   emp42 emp43 emp44 emp45 emp46 emp47 emp48 emp49 emp50 emp51 emp52
## 1    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA
## 2    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA
## 3    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA    NA
## 4     1     1     1     1     1     1     1     1     1     1     1
##   subject
## 1       1
## 2       2
## 3       3
## 4       4
```

to long format

```
##   subject calendar.week start stop arrest employed fin age race wexp mar
## 1       1             1     0    1      0        0   0  27    1    0   0
## 2       1             2     1    2      0        0   0  27    1    0   0
## 3       1             3     2    3      0        0   0  27    1    0   0
## 4       1             4     3    4      0        0   0  27    1    0   0
##   paro prio educ
## 1    1    3    3
## 2    1    3    3
## 3    1    3    3
## 4    1    3    3
```

We yield the same Coefficients for both data sets if we include only the time-constant predictors:

```
## Call:
## coxph(formula = Surv(week, arrest) ~ fin + age + mar + prio,
##     data = prison.short, method = "efron")
##
##         coef exp(coef) se(coef)     z       p
## fin  -0.3602    0.6975   0.1905 -1.89 0.05864
## age  -0.0604    0.9414   0.0209 -2.90 0.00376
## mar  -0.5331    0.5868   0.3728 -1.43 0.15266
## prio  0.0975    1.1024   0.0272  3.58 0.00034
##
## Likelihood ratio test=31.4  on 4 df, p=2.53e-06
## n= 432, number of events= 114
```

```
## Call:
## coxph(formula = Surv(start, stop, arrest) ~ fin + age + mar +
##     prio, data = prison.long)
##
##         coef exp(coef) se(coef)     z       p
```

```
## fin  -0.3602    0.6975   0.1905 -1.89 0.05864
## age  -0.0604    0.9414   0.0209 -2.90 0.00376
## mar  -0.5331    0.5868   0.3728 -1.43 0.15266
## prio  0.0975    1.1024   0.0272  3.58 0.00034
##
## Likelihood ratio test=31.4  on 4 df, p=2.53e-06
## n= 19809, number of events= 114
```

Now we include the time-varying employment variable:

```
## Call:
## coxph(formula = Surv(start, stop, arrest) ~ fin + age + prio +
##     mar + employed, data = prison.long)
##
##             coef exp(coef) se(coef)     z      p
## fin      -0.3390    0.7125   0.1904 -1.78 0.0750
## age      -0.0460    0.9551   0.0206 -2.23 0.0255
## prio      0.0842    1.0878   0.0278  3.03 0.0024
## mar      -0.3612    0.6968   0.3733 -0.97 0.3333
## employed -1.3290    0.2647   0.2498 -5.32  1e-07
##
## Likelihood ratio test=67.2  on 5 df, p=3.87e-13
## n= 19809, number of events= 114
```

11 Time discrete Survival models

Discretize time in intervals $[a_0, a_1[, ..., [a_{q-1}, a_q[$ and fit classic GLM's **without** an intercept on the transformed data with the event variable as response. The coefficients of the time variables are used as intercepts.

11.1 Data

We add the time variable `t` as a factor to our data frame

```
##   subject calendar.week start stop arrest employed fin age race wexp mar
## 1       1             1     0    1      0        0   0  27    1    0   0
## 2       1             2     1    2      0        0   0  27    1    0   0
## 3       1             3     2    3      0        0   0  27    1    0   0
## 4       1             4     3    4      0        0   0  27    1    0   0
## 5       1             5     4    5      0        0   0  27    1    0   0
## 6       1             6     5    6      0        0   0  27    1    0   0
##   paro prio educ t
## 1    1    3    3 1
## 2    1    3    3 2
## 3    1    3    3 3
## 4    1    3    3 4
## 5    1    3    3 5
## 6    1    3    3 6
```

11.2 Model

Fit a logit-model on the data with `t` as input. The hazard in the logit model follows: and thus the baseline hazard (all other coavariates than the time dummy-variable of interest):

Thus, we yield 52 time coeffients next to the other coefficients:

```
##
## Call:
## glm(formula = arrest ~ -1 + t + fin + age + mar + prio, family = binomial(link = "logit"),
##     data = prison.long)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -0.3929  -0.1236  -0.0930  -0.0669   3.8088
##
## Coefficients:
##       Estimate Std. Error z value Pr(>|z|)
## t1    -4.78099    1.11448  -4.290 1.79e-05 ***
## t2    -4.77850    1.11458  -4.287 1.81e-05 ***
## t3    -4.77779    1.11446  -4.287 1.81e-05 ***
## t4    -4.77595    1.11435  -4.286 1.82e-05 ***
## t5    -4.77283    1.11452  -4.282 1.85e-05 ***
## t6    -4.76924    1.11466  -4.279 1.88e-05 ***
## t7    -4.76440    1.11479  -4.274 1.92e-05 ***
## t8    -3.13959    0.66561  -4.717 2.39e-06 ***
## t9    -4.05164    0.86167  -4.702 2.58e-06 ***
## t10   -4.74558    1.11454  -4.258 2.06e-05 ***
## t11   -4.03949    0.86129  -4.690 2.73e-06 ***
## t12   -4.02106    0.86105  -4.670 3.01e-06 ***
## t13   -4.71502    1.11415  -4.232 2.32e-05 ***
## t14   -3.60635    0.75813  -4.757 1.97e-06 ***
## t15   -4.00111    0.86115  -4.646 3.38e-06 ***
## t16   -3.99587    0.86127  -4.640 3.49e-06 ***
## t17   -3.58399    0.75803  -4.728 2.27e-06 ***
## t18   -3.56763    0.75836  -4.704 2.55e-06 ***
## t19   -3.96549    0.86152  -4.603 4.17e-06 ***
## t20   -3.03273    0.66548  -4.557 5.18e-06 ***
## t21   -3.94828    0.86169  -4.582 4.60e-06 ***
## t22   -4.64070    1.11449  -4.164 3.13e-05 ***
## t23   -4.63504    1.11454  -4.159 3.20e-05 ***
## t24   -3.23726    0.70175  -4.613 3.97e-06 ***
## t25   -3.52033    0.75851  -4.641 3.47e-06 ***
## t26   -3.49480    0.75737  -4.614 3.94e-06 ***
## t27   -3.89779    0.86017  -4.531 5.86e-06 ***
## t28   -3.89186    0.86015  -4.525 6.05e-06 ***
## t29  -18.19320  547.40235  -0.033 0.973487
## t30   -3.88282    0.86034  -4.513 6.39e-06 ***
## t31   -4.57306    1.11385  -4.106 4.03e-05 ***
## t32   -3.87112    0.86090  -4.497 6.90e-06 ***
## t33   -3.86440    0.86123  -4.487 7.22e-06 ***
## t34   -3.85163    0.86151  -4.471 7.79e-06 ***
## t35   -3.14353    0.70153  -4.481 7.43e-06 ***
## t36   -3.42146    0.75910  -4.507 6.57e-06 ***
## t37   -3.12107    0.70258  -4.442 8.90e-06 ***
## t38   -4.50319    1.11496  -4.039 5.37e-05 ***
## t39   -3.80263    0.86223  -4.410 1.03e-05 ***
## t40   -3.09650    0.70259  -4.407 1.05e-05 ***
## t41  -18.16530  568.23431  -0.032 0.974498
```

```
## t42   -3.77967    0.86300  -4.380 1.19e-05 ***
## t43   -3.07561    0.70369  -4.371 1.24e-05 ***
## t44   -3.75914    0.86375  -4.352 1.35e-05 ***
## t45   -3.75108    0.86412  -4.341 1.42e-05 ***
## t46   -3.04004    0.70544  -4.309 1.64e-05 ***
## t47   -4.42745    1.11689  -3.964 7.37e-05 ***
## t48   -3.72618    0.86470  -4.309 1.64e-05 ***
## t49   -2.78833    0.66969  -4.164 3.13e-05 ***
## t50   -3.29221    0.76310  -4.314 1.60e-05 ***
## t51  -18.14517  589.76136  -0.031 0.975455
## t52   -2.98335    0.70667  -4.222 2.42e-05 ***
## fin   -0.36333    0.19143  -1.898 0.057692 .
## age   -0.06071    0.02092  -2.902 0.003706 **
## mar   -0.53659    0.37384  -1.435 0.151186
## prio   0.09836    0.02745   3.584 0.000339 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##     Null deviance: 27461  on 19809  degrees of freedom
## Residual deviance:  1325  on 19753  degrees of freedom
## AIC: 1437
##
## Number of Fisher Scoring iterations: 18
```

11.3 Smooth time variables

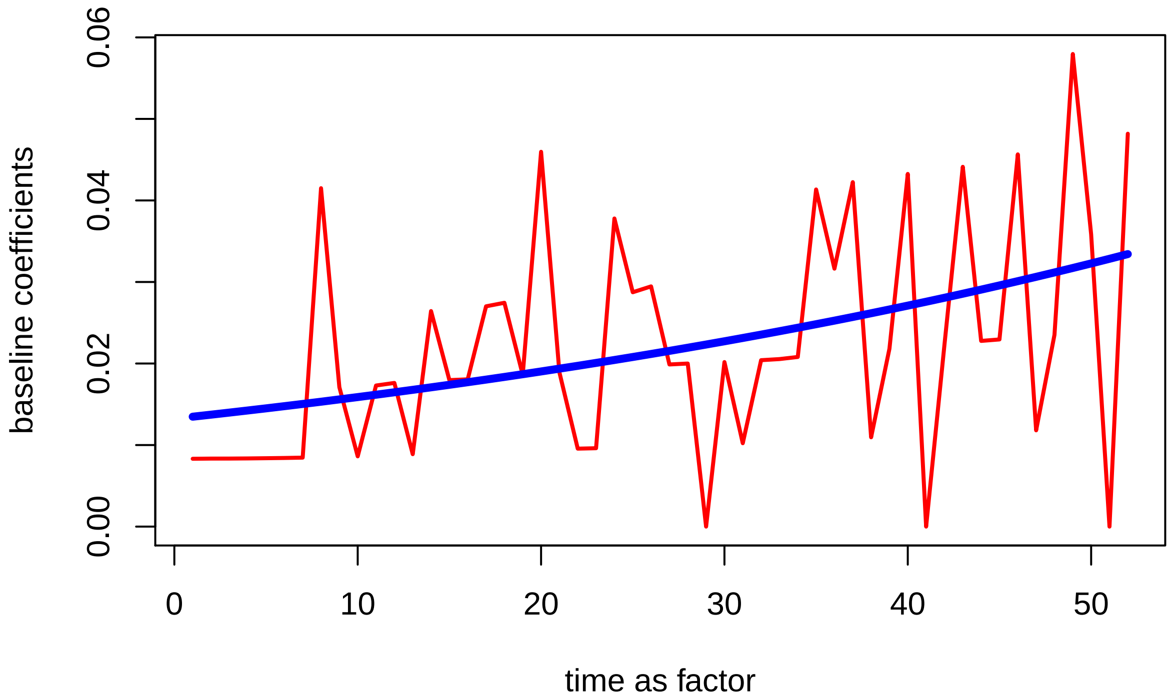
We include the time variable via a smoothing spline and yield a sparser model with more or less the same coefficients for our covariates:

```
##
## Family: binomial
## Link function: logit
##
## Formula:
## arrest ~ s(stop) + fin + age + mar + prio
##
## Parametric coefficients:
##             Estimate Std. Error z value Pr(>|z|)
## (Intercept) -3.85034    0.49838  -7.726 1.11e-14 ***
## fin         -0.36353    0.19120  -1.901 0.057269 .
## age         -0.06052    0.02090  -2.896 0.003780 **
## mar         -0.53563    0.37359  -1.434 0.151646
## prio         0.09800    0.02739   3.578 0.000346 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Approximate significance of smooth terms:
##           edf Ref.df Chi.sq p-value
## s(stop) 1.024  1.047  8.271 0.00473 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
```

```
## R-sq.(adj) =  0.00223   Deviance explained =  2.7%
## UBRE = -0.93047  Scale est. = 1         n = 19809
```

We cannot interpret those baseline hazards in a reasonable manner.

Graphically, we see that the baseline hazards from the blue, spline curve is much smoother and less “outlier-sensitive” (e.g.: time points without events), than from the simple logit model in red:



12 Piecewise exponential models (PEM)

12.0.1 Model equation:

$$\lambda_i(t|x_i) = \lambda_j exp(x^T\beta), \forall t \in]a_{j-1}, a_j]$$

with constant baseline hazards in each of the J intervals.

12.0.2 Data

```
##   id tstart tend interval offset ped_status treatment pair
## 1  1      0    1    (0,1]      0          1   placebo    1
## 2  2      0    1    (0,1]      0          0      6-MP    1
## 3  2      1    2    (1,2]      0          0      6-MP    1
## 4  2      2    3    (2,3]      0          0      6-MP    1
## 5  2      3    4    (3,4]      0          0      6-MP    1
## 6  2      4    5    (4,5]      0          0      6-MP    1
```

We fit an intercept-only model for many intervals resulting in many baseline intercepts:

```
##
## Call:
## glm(formula = ped_status ~ interval - 1, family = poisson(link = log),
```

```
##     data = leuk.ped, offset = offset)
##
## Deviance Residuals:
##     Min       1Q   Median       3Q      Max
## -0.7559  -0.3780  -0.3162  -0.2294   2.3082
##
## Coefficients:
##                  Estimate Std. Error z value Pr(>|z|)
## interval(0,1]     -3.0445     0.7071  -4.306 1.67e-05 ***
## interval(1,2]     -2.9957     0.7071  -4.237 2.27e-05 ***
## interval(2,3]     -3.6376     1.0000  -3.638 0.000275 ***
## interval(3,4]     -2.9178     0.7071  -4.126 3.69e-05 ***
## interval(4,5]     -2.8622     0.7071  -4.048 5.17e-05 ***
## interval(5,6]     -2.3979     0.5774  -4.153 3.28e-05 ***
## interval(6,7]     -3.3673     1.0000  -3.367 0.000759 ***
## interval(7,8]     -1.9459     0.5000  -3.892 9.95e-05 ***
## interval(8,9]    -19.3026  1924.2001  -0.010 0.991996
## interval(9,10]    -3.1355     1.0000  -3.135 0.001716 **
## interval(10,11]   -2.3514     0.7071  -3.325 0.000883 ***
## interval(11,12]   -2.1972     0.7071  -3.107 0.001888 **
## interval(12,13]   -2.7726     1.0000  -2.773 0.005561 **
## interval(13,15]   -3.4012     1.0000  -3.401 0.000671 ***
## interval(15,16]   -2.6391     1.0000  -2.639 0.008314 **
## interval(16,17]   -2.5649     1.0000  -2.565 0.010319 *
## interval(17,19]  -19.9957  2842.2319  -0.007 0.994387
## interval(19,20]  -19.3026  2980.9580  -0.006 0.994833
## interval(20,22]   -2.1972     0.7071  -3.107 0.001888 **
## interval(22,23]   -1.2528     0.7071  -1.772 0.076449 .
## interval(23,25]  -19.9957  4215.7112  -0.005 0.996216
## interval(25,32]  -21.2485  4713.3084  -0.005 0.996403
## interval(32,34]  -19.9957  6665.6247  -0.003 0.997606
## interval(34,35]  -19.3026  9426.6168  -0.002 0.998366
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for poisson family taken to be 1)
##
##     Null deviance: 1017.84  on 475  degrees of freedom
## Residual deviance:  148.11  on 451  degrees of freedom
## AIC: 256.11
##
## Number of Fisher Scoring iterations: 17
```

- we fit way too many parameters
- intervals which did not face events have super high standard errors and strange coefficients
- -> Two reasons for fitting PAM's with smooth baseline hazards

13 Piecewise additive exponential models (PAM)

New compared to PEM: smooth modeling of the piecewise constant baseline hazards e.g. via splines. Cool because:

- PEM constrained by use of intervals as high J leads to parameter explosion

- Smoother curves due to penalization of splines on the overlaps of the intervals
- Problem PEM: no data in interval $]a_{l-1}, a_l]$ -> $\lambda_l = 0$, wiggely hazard rate curves

13.0.1 Model equation:

$$\lambda_i(t|x_i) = exp(f_0(t_j) + x^T\beta)$$

with spline for time dependent baseline hazard:

$$f_0(t_j) = log(\lambda_0(t_j)) = \sum_{k=1}^{K} \gamma_k B_k(t_j)$$

and for time varying covariates:

$$\lambda_i(t|x_i) = exp(f_0(t_j) + \sum_{j=1}^{p} f_k(x_i, k))$$

14 Piecewise additive exponential mixed models (PAMM)

14.0.1 Model equation:

$$\lambda_i(t|x_i) = exp(f_0(t_j) + x^T\beta)$$

with spline for time dependent baseline hazard:

$$f_0(t_j) = log(\lambda_0(t_j)) = \sum_{k=1}^{K} \gamma_k B_k(t_j)$$

and for time varying covariates:

$$\lambda_i(t|x_i) = exp(f_0(t_j) + \sum_{j=1}^{p} f_k(x_i, k))$$

14.0.2 Data

looks like that:

```
##   CombinedID tstart tend interval offset ped_status CombinedicuID Year Age
## 1       1101      4    5    (4,5]      0          0          1114 2007  71
## 2       1101      5    6    (5,6]      0          0          1114 2007  71
## 3       1101      6    7    (6,7]      0          0          1114 2007  71
## 4       1101      7    8    (7,8]      0          0          1114 2007  71
## 5       1101      8    9    (8,9]      0          0          1114 2007  71
## 6       1101      9   10   (9,10]      0          0          1114 2007  71
##        BMI AdmCatID DiagID2 ApacheIIScore DaysInICU
## 1 38.97392  Medical  Sepsis            13  6.743056
## 2 38.97392  Medical  Sepsis            13  6.743056
## 3 38.97392  Medical  Sepsis            13  6.743056
## 4 38.97392  Medical  Sepsis            13  6.743056
## 5 38.97392  Medical  Sepsis            13  6.743056
## 6 38.97392  Medical  Sepsis            13  6.743056
```

Fit a PAMM with a smooth spline term for time (tend) and the other continous variables using this formula:

```
pamm_icu <- bam(ped_status ~ s(tend) + Year + AdmCatID + DiagID2 + s(Age) + s(BMI) +
      s(ApacheIIScore) + s(CombinedicuID, bs="re"), offset=offset, data = ped,
    family=poisson(), discrete = TRUE)
```

We include the variable CombinedicuID as a random effect aka as a **frailty term**. Therefore wie use `bs = "re"`. We control for the random effects of the ICU units without having to model a dummy for each of the ICU's. The frailty model just estimates a Gaussian over the different ICU's for which we only have to estimate the variance: 1 parameter vs. 400.

We model the PAM as a Poisson model with log link on the death-indicator `ped_status`

This is the model summary:

```
##
## Family: poisson
## Link function: log
##
## Formula:
## ped_status ~ s(tend) + Year + AdmCatID + DiagID2 + s(Age) + s(BMI) +
##     s(ApacheIIScore) + s(CombinedicuID, bs = "re")
##
## Parametric coefficients:
##                              Estimate Std. Error z value Pr(>|z|)
## (Intercept)                  -4.59863    0.11388 -40.383  < 2e-16 ***
## Year2008                      0.02718    0.07425   0.366 0.714314
## Year2009                     -0.08622    0.07466  -1.155 0.248156
## Year2011                     -0.02329    0.06966  -0.334 0.738144
## AdmCatIDSurgical Elective    -0.47450    0.09297  -5.104 3.33e-07 ***
## AdmCatIDSurgical Emergency -0.25668    0.07228  -3.551 0.000384 ***
## DiagID2Cardio-Vascular        0.12439    0.08721   1.426 0.153774
## DiagID2Other                  0.10391    0.12855   0.808 0.418914
## DiagID2Metabolic             -0.92768    0.25552  -3.631 0.000283 ***
## DiagID2Neurologic             0.01267    0.09508   0.133 0.893972
## DiagID2Orthopedic/Trauma     -0.26816    0.11560  -2.320 0.020354 *
## DiagID2Renal                 -0.02734    0.21580  -0.127 0.899183
## DiagID2Respiratory           -0.13289    0.08618  -1.542 0.123091
## DiagID2Sepsis                 0.05627    0.09895   0.569 0.569587
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Approximate significance of smooth terms:
##                        edf  Ref.df Chi.sq  p-value
## s(tend)              1.000   1.001 248.94  < 2e-16 ***
## s(Age)               1.002   1.003 122.98  < 2e-16 ***
## s(BMI)               3.061   3.879  40.61 3.55e-08 ***
## s(ApacheIIScore)     1.890   2.422 163.17  < 2e-16 ***
## s(CombinedicuID) 101.279 363.000 152.16 3.35e-08 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## R-sq.(adj) =  -0.00897   Deviance explained =  -15%
## fREML = 2.0196e+05  Scale est. = 1         n = 208536
```

14.0.3 What can we say?

- smooth terms for continuos variables:
  - if the edf (estimated degress of freedom) = 1, our spline smoother estimated the variable as a linear effect on the hazard rate. This is the case for Age and time

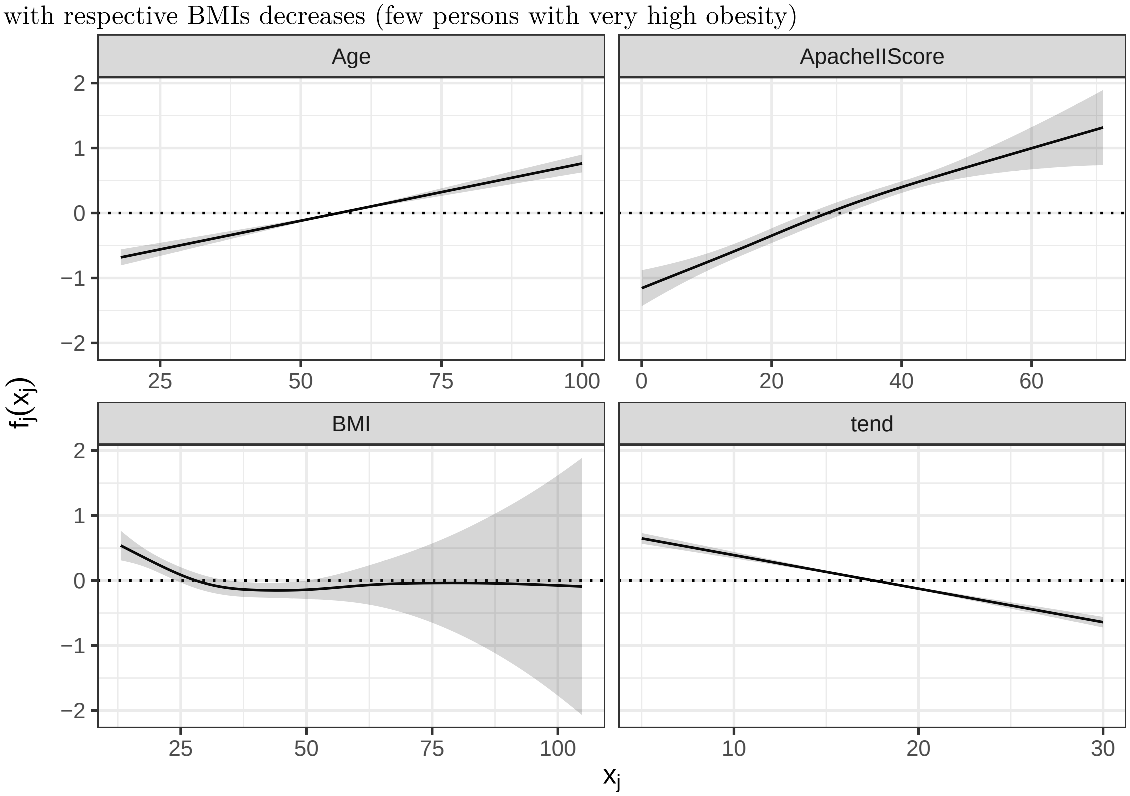
  - BMI, ApacheIIScore and CombinedicuID (only frailty effect) seem to have a non-linear effect on the hazard rate

  - HOW TO INTERPRET SPLINE FOR COMBINEDICUID FRAILTY @ ANDREAS
  - those effects can also be seen graphically which shows the effect of the variable's values on the linear predictor aka the log(hazard-rate). This is the exact value that enters our linear predictor, e.g. 75 year old person enters 0.3
  - time (tend) has a falling slope aka a decreasing effect on the log(hazard) -> has hazard decreases also

  - ApacheIIScore has almost linear effect: (log-) hazard increases with increasing Apache Scores though this increase is getting lower with higher values of the score

  - increasing linear age effect, the older, the higher the (log-)hazard

  - typical shape of the BMI effect, very low BMIs have increased hazard, that decreases toward "normal" BMIs, high uncertainty with respect to effect of very high BMIs as number of patients with respective BMIs decreases (few persons with very high obesity)



- non-smooth terms for categorical variables:
  - exponentiate the coefficients `exp(beta)` and interpret their **mulitplicative** effect on the hazard rate w.r.t the reference category

  - example 1: hazard rate for a person treated in 2009 is exp(-0.08622441) = 0.9173883 times as high as the hazard rate for similar person treated in 2007 (reference category)

- example 2: hazard rate for a person with Metabolic cancer is exp(-0.92767602) = 0.3954717 times as high as the hazard rate for similar person with Gastrointestinal cancer (reference category)
- For more, interpret this table:

```
##                                    beta        HR
## Year2008                     0.02718222 1.0275550
## Year2009                    -0.08622441 0.9173883
## Year2011                    -0.02328905 0.9769801
## AdmCatIDSurgical Elective   -0.47449956 0.6221964
## AdmCatIDSurgical Emergency -0.25667793 0.7736173
## DiagID2Cardio-Vascular       0.12438947 1.1324568
## DiagID2Other                 0.10391129 1.1095020
## DiagID2Metabolic            -0.92767602 0.3954717
## DiagID2Neurologic            0.01267184 1.0127525
## DiagID2Orthopedic/Trauma    -0.26815998 0.7647854
## DiagID2Renal                -0.02733998 0.9730304
## DiagID2Respiratory          -0.13289109 0.8755604
## DiagID2Sepsis                0.05627062 1.0578839
```

15 Frailty models

16 Aalen model

16.0.1 model equation

$$\lambda(t) = \lambda_0(t) + x'(t)\beta(t) = \sum_{k=1}^{p} x_k(t)\beta_k(t)$$

with additive effects of time-varying covariates on baseline hazard rate

16.0.2 Data

16.0.3 Data

looks like that

```
##   major_complications age charlson_score sex transfusion metastasesYN
## 1                  no  58              2   f         yes            1
## 2                 yes  52              2   m          no            1
## 3                  no  74              2   f         yes            1
## 4                 yes  57              2   m         yes            1
## 5                  no  30              2   f         yes            1
## 6                  no  66              2   f         yes            1
##   major_resection days status id metastases
## 1              no  579      0  1        yes
## 2              no 1192      0  2        yes
## 3              no  308      1  3        yes
## 4             yes   33      1  4        yes
## 5             yes  397      1  5        yes
## 6             yes 1219      0  6        yes
```

16.0.4 Simple additive aalen model form lecture

```
## Additive Aalen Model
##
## Test for nonparametric terms
##
## Test for non-significant effects
##                          Supremum-test of significance p-value H_0: B(t)=0
## (Intercept)                                       4.24               0.000
## age                                               4.35               0.000
## charlson_score                                    4.21               0.001
## major_complicationsyes                            7.14               0.000
## metastasesyes                                     3.41               0.021
##
## Test for time invariant effects
##                                Kolmogorov-Smirnov test
## (Intercept)                                    0.60900
## age                                            0.00636
## charlson_score                                 0.22700
## major_complicationsyes                         0.29400
## metastasesyes                                  0.37300
##                          p-value H_0:constant effect
## (Intercept)                                    0.221
## age                                            0.546
## charlson_score                                 0.041
## major_complicationsyes                         0.146
## metastasesyes                                  0.039
##                                  Cramer von Mises test
## (Intercept)                                    420.000
## age                                              0.027
## charlson_score                                  54.700
## major_complicationsyes                          89.000
## metastasesyes                                  166.000
##                          p-value H_0:constant effect
## (Intercept)                                    0.101
## age                                            0.508
## charlson_score                                 0.017
## major_complicationsyes                         0.073
## metastasesyes                                  0.018
##
##
##
##   Call:
## aalen(formula = Surv(days, status) ~ age + charlson_score + major_complications +
##     metastases, data = liver, residuals = 1)
```

- DISCUSS interpretation for tests (supremum, Kolmogorov Smirnoff)
- huhuh

17 Cox-Aalen model

17.0.1 model equation

$$\lambda(t) = \lambda_0(t) + X(t)\beta(t) \cdot exp(Z(t)'\gamma)$$

with additive effects of time-varying covariates on baseline hazard rate which are also multiplicatively affected via Cox part of the model. γ are time-constant coefficients, PH-assumption, and β are time varying additive coefficients by the Aalen-part.

17.0.2 Data

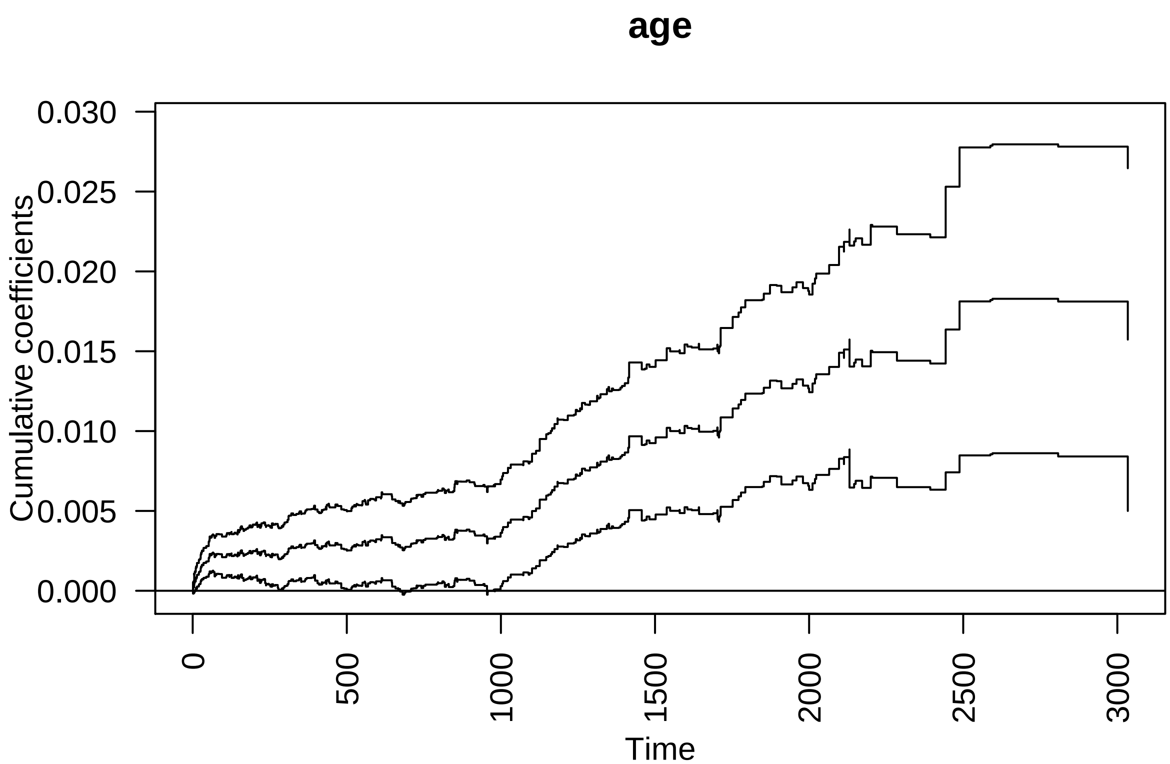
looks like that

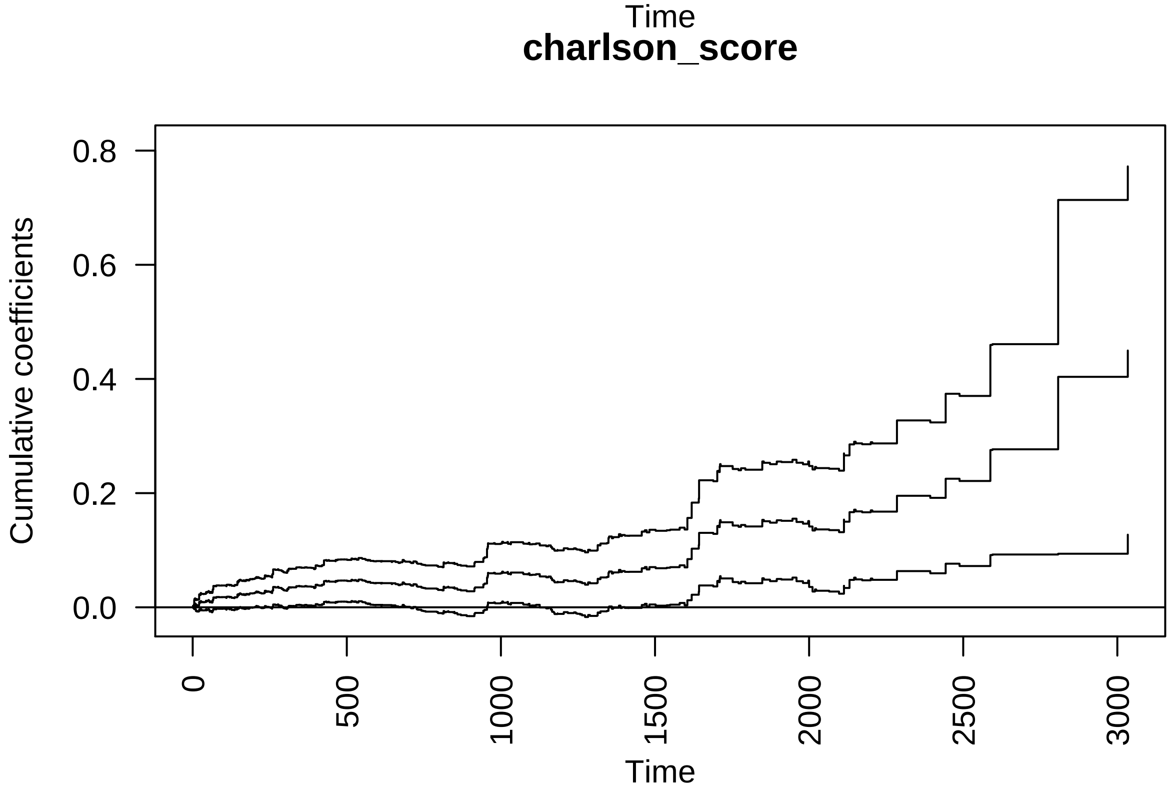
```
##   major_complications age charlson_score sex transfusion metastasesYN
## 1                  no  58              2   f         yes            1
## 2                 yes  52              2   m          no            1
## 3                  no  74              2   f         yes            1
## 4                 yes  57              2   m         yes            1
## 5                  no  30              2   f         yes            1
## 6                  no  66              2   f         yes            1
##   major_resection days status id metastases
## 1              no  579      0  1        yes
## 2              no 1192      0  2        yes
## 3              no  308      1  3        yes
## 4             yes   33      1  4        yes
## 5             yes  397      1  5        yes
## 6             yes 1219      0  6        yes
```

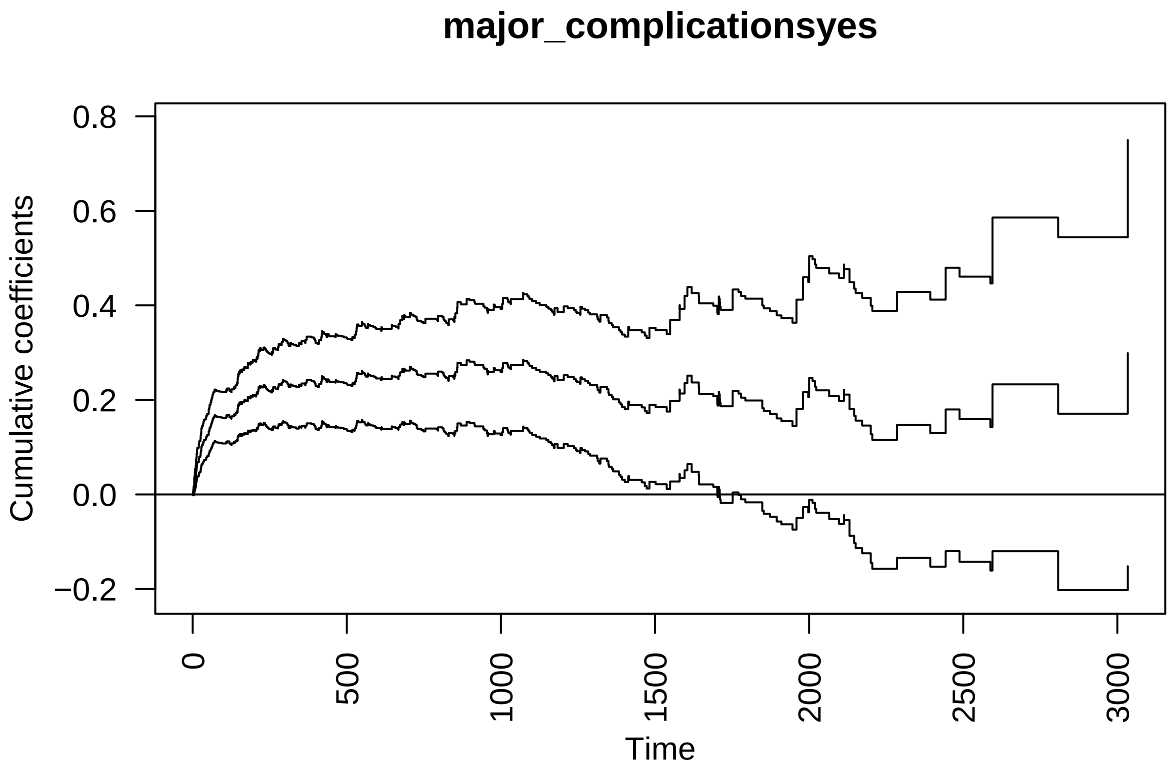
17.0.3 What can we say from the graphic?

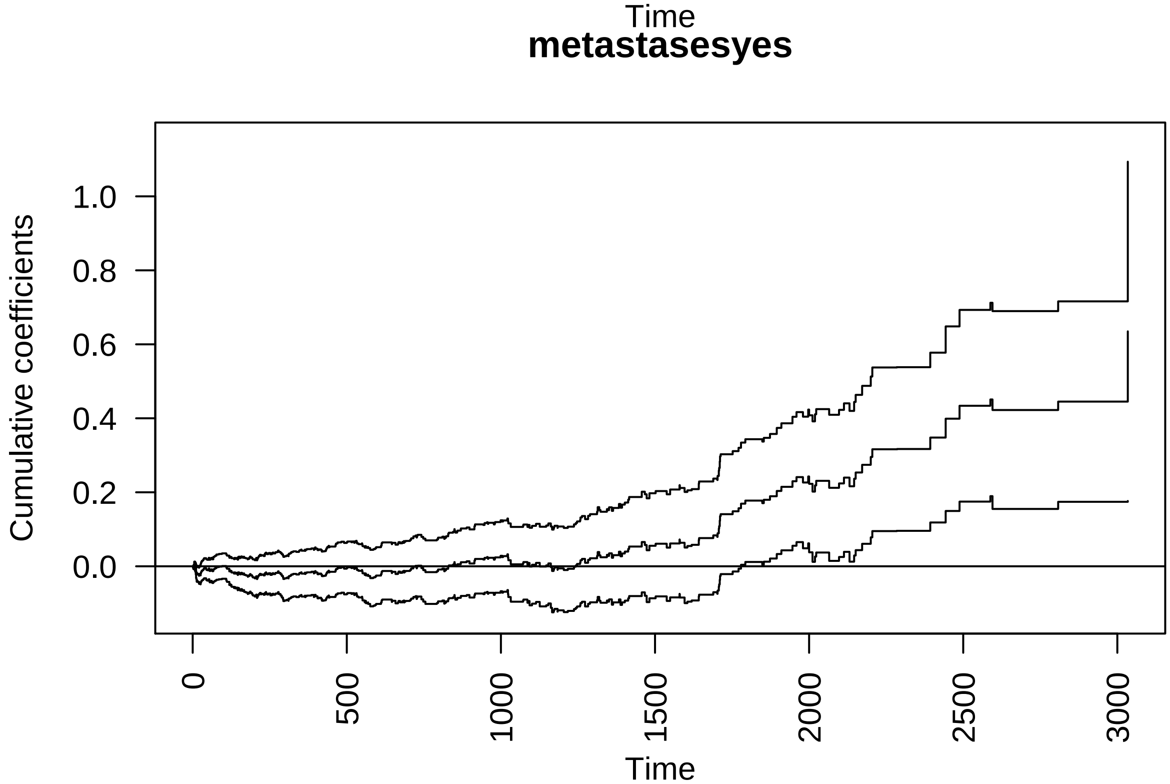
- Age:
  - the cumulative Hazard of a person aged A+1 at time point t = 1500 is 0.01 higher than that of a person aged A
  - the effect of metastases on the cumulative hazard rate starts to increase t = 1000 after the surgery and is approx. constant before
- Complications:
  - the cumulative Hazard of a person with major complications at time point t = 1500 is 0.2 higher than that of a person without complications
  - the effect of complications on the cumulative hazard rate decreases over time
- Metastases:
  - the cumulative Hazard of a person with metastases at time point t = 2500 is 0.4 higher than that of a person without metastases
  - the effect of metastases on the cumulative hazard rate starts to matter only after t = 1500 and then increases more or less linearly
  - before t = 1500 the effect is non siginificant as the 0 is part of the confidence intervals

Effects for the continous variables estimated as additive via the Aalen-part of the model using the formula `Surv(days, status) ~ age +  charlson_score + major_complications + metastases + prop(sex) + prop(transfusion) + prop(major_resection), data = liver, residuals = 1, basesim   = 1)`


age
Cumulative coefficients
0.030
0.025
0.020
0.015
0.010
0.005
0.000
0
500
1000
1500
2000
2500
3000
Time


charlson_score
Cumulative coefficients
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
2000
2500
3000
Time





17.0.4 What can we say from the model summary?

```
## Cox-Aalen Model
##
## Test for Aalen terms
```

```
## Test for nonparametric terms
##
## Test for non-significant effects
##                         Supremum-test of significance p-value H_0: B(t)=0
## (Intercept)                                      4.00              0.000
## age                                              4.18              0.002
## charlson_score                                   4.04              0.000
## major_complicationsyes                           6.07              0.000
## metastasesyes                                    3.85              0.002
##
## Test for time invariant effects
##                               Kolmogorov-Smirnov test
## (Intercept)                                   0.43700
## age                                           0.00522
## charlson_score                                0.16400
## major_complicationsyes                        0.21200
## metastasesyes                                 0.28100
##                         p-value H_0:constant effect
## (Intercept)                                   0.218
## age                                           0.396
## charlson_score                                0.104
## major_complicationsyes                        0.148
## metastasesyes                                 0.012
##
## Proportional Cox terms :
##                           Coef.    SE Robust SE D2log(L)^-1    z  P-val
## prop(sex)f                0.224 0.111     0.107       0.109 2.08 0.0373
## prop(transfusion)yes      0.233 0.111     0.113       0.112 2.07 0.0386
## prop(major_resection)yes 0.254 0.113     0.110       0.113 2.31 0.0207
##                           lower2.5% upper97.5%
## prop(sex)f                  0.00644      0.442
## prop(transfusion)yes        0.01540      0.451
## prop(major_resection)yes   0.03250      0.475
## Test of Proportionality
##                           sup|  hat U(t) | p-value H_0
## prop(sex)f                           9.53        0.204
## prop(transfusion)yes                 6.51        0.550
## prop(major_resection)yes             8.99        0.214
```

- Aalen part:
  - Supremum-test: for all 4 variables the H0: no effect can be rejected
  - Kolmogorov Smirnov for time variant effects: H0: constant effect can only clearly be rejected for metastases DISCUSS THIS
- Cox part:
  - sexf: the additive, time-varying effects $\beta(t) = (\beta_{age}(t), \beta_{charlson}(t), \beta_{complications}(t), \beta_{metastases}(t))^T$ from the Aalen model is getting multiplied by factor $exp(0.224) = 1.251071$ for a female compared with a similar man
  - same for transfusion (exp(0.233) = 1.262381) and major_resection (exp(0.254) = 1.289172)
  - DISCUSS

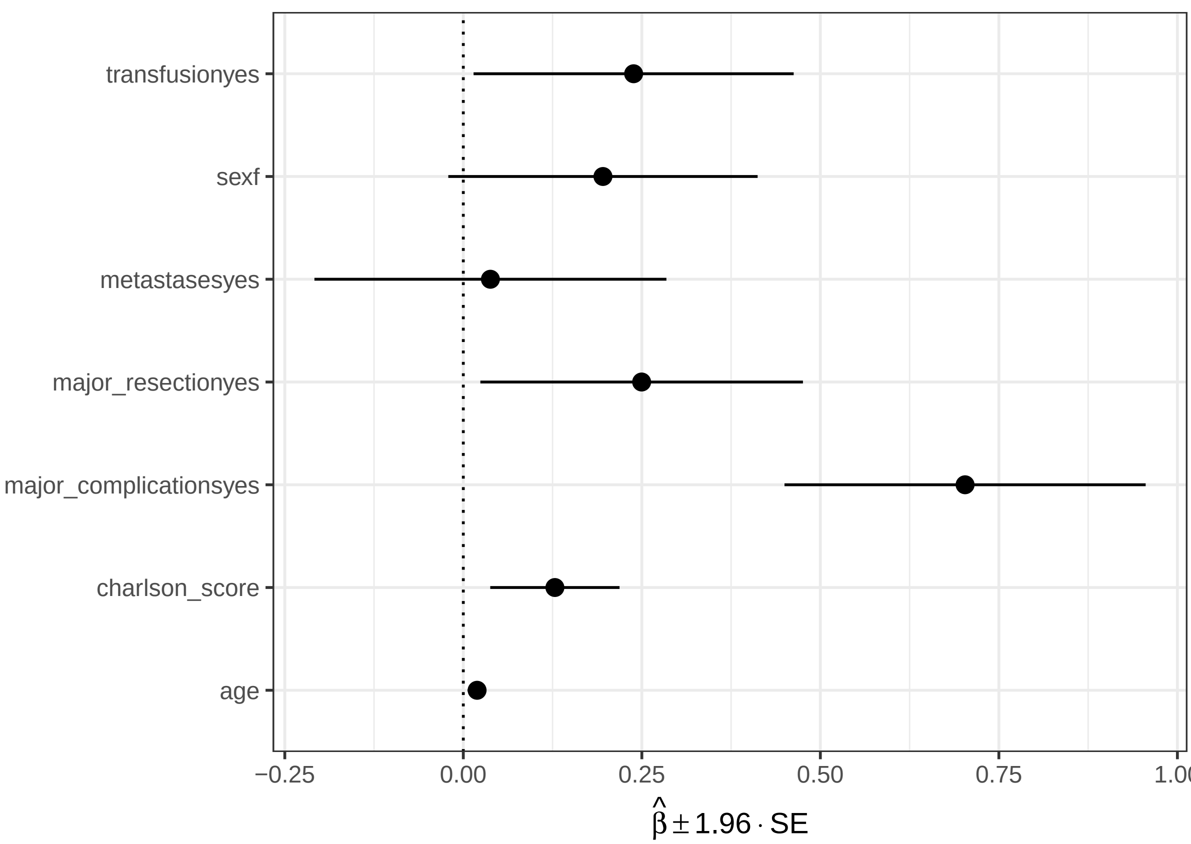
17.0.5 Cox-Aalen vs. PAM

Compare this with the PAM fitted on the data using the below formula. We explicitly model time varying effects of the 4 variables (metastases, marjo_complications, age, charlson) as in the Aalen model via ti().

```
bam(
  formula = ped_status ~ ti(tend,k=10) +
    # use ti() for non-identifiability issue
    metastases + ti(tend, by = as.ordered(metastases),k=10, mc = c(1,0)) +
    major_complications + ti(tend,by = as.ordered(major_complications),k=10, mc = c(1,0)) +
    age + ti(tend, by = age,k=10, mc = c(1,0)) +
    charlson_score + ti(tend, by = charlson_score,k=10, mc = c(1,0)) +
    sex + transfusion + major_resection,
  data   = ped_liver,
  offset = offset,
  family = poisson())
```

The figure below shows the effect of the **time constant variables** which allow some interpretation:

- NOTE: Constant contributions to time-varying can be interpreted as effects at t=0. Check the model equation and DISCUSS
- sex: Compared to males, females have a 1.22 times increased risk of experiencing an event (c.p.)
- transfusion: Compared to patients without transfusion, patients with transfustion have a 1.27 times increased risk of experiencing an event (c.p.)
- major resection: A major resection increases the risk of event by a factor of 1.28, compared to patients without a major resection
- DISCUSS If above interpretation holds, this would fit nicely the effect of the time-constant factors in the Cox-part of above Cox-Aalen model

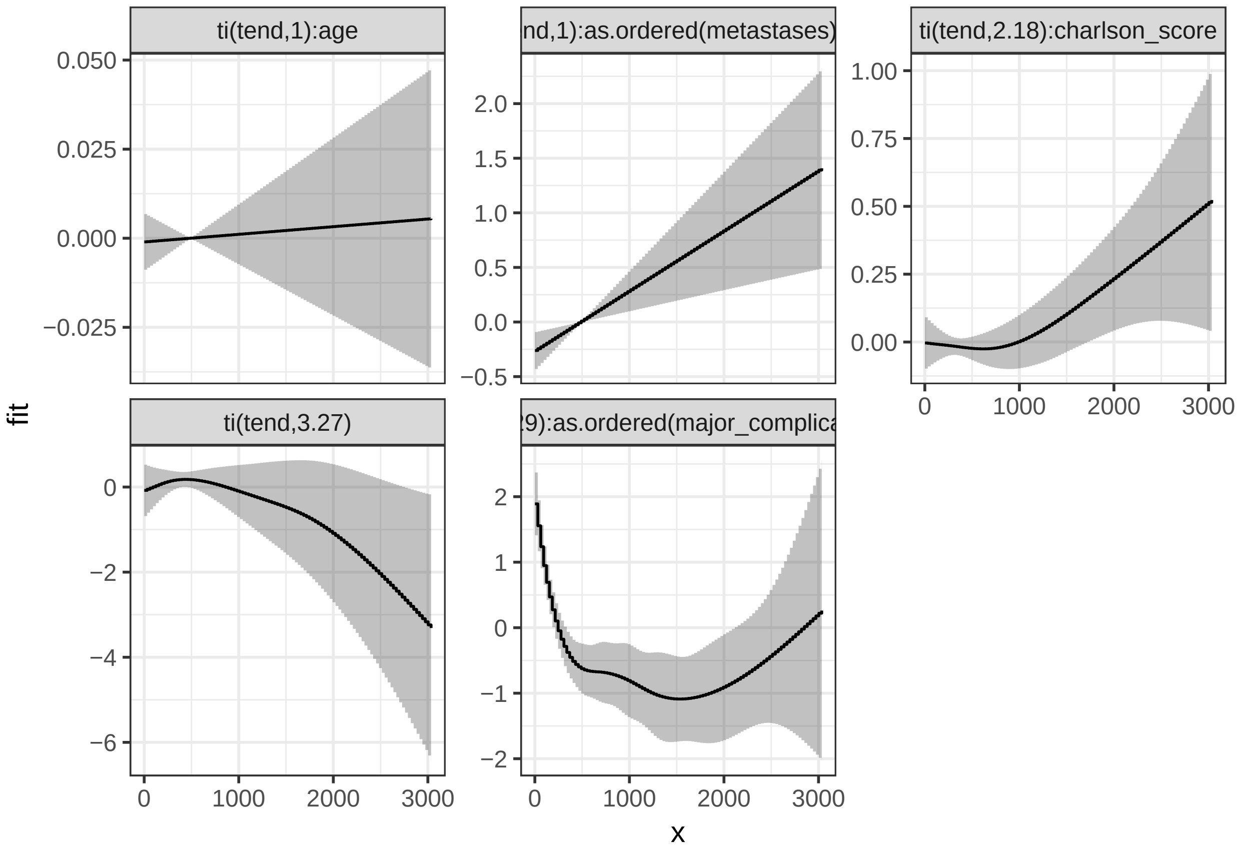


Model summary:

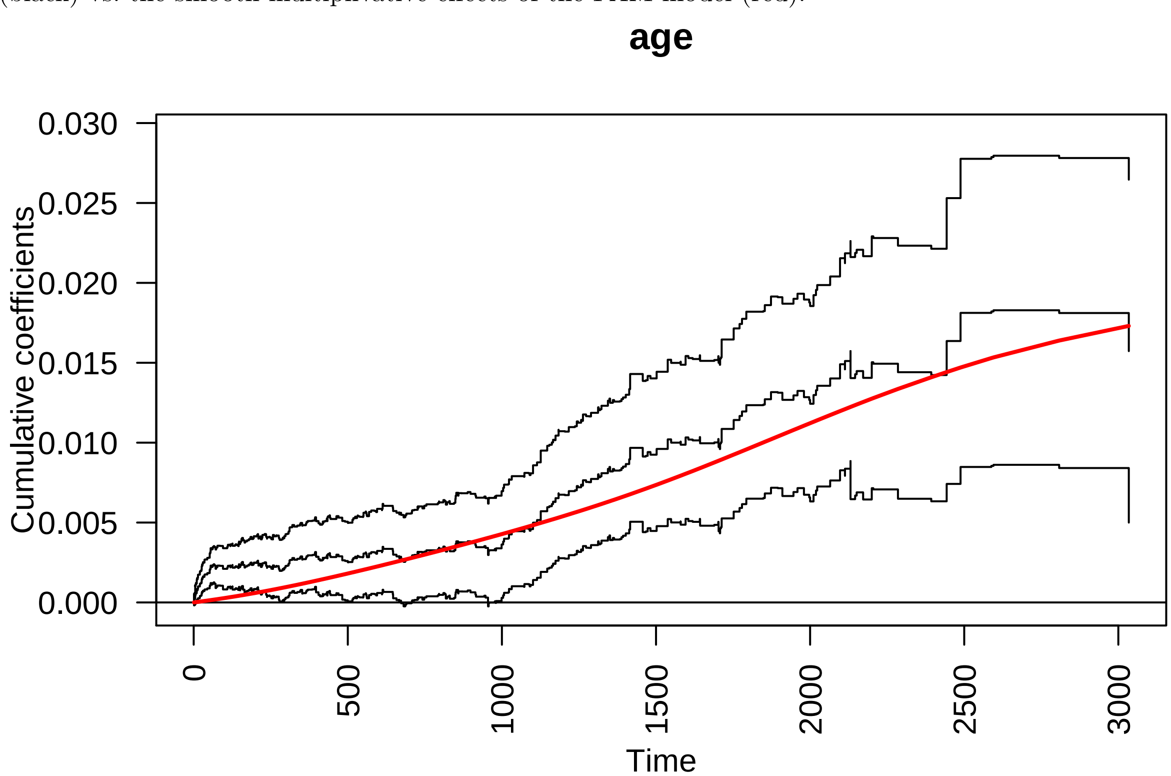
```
##
## Family: poisson
## Link function: log
```

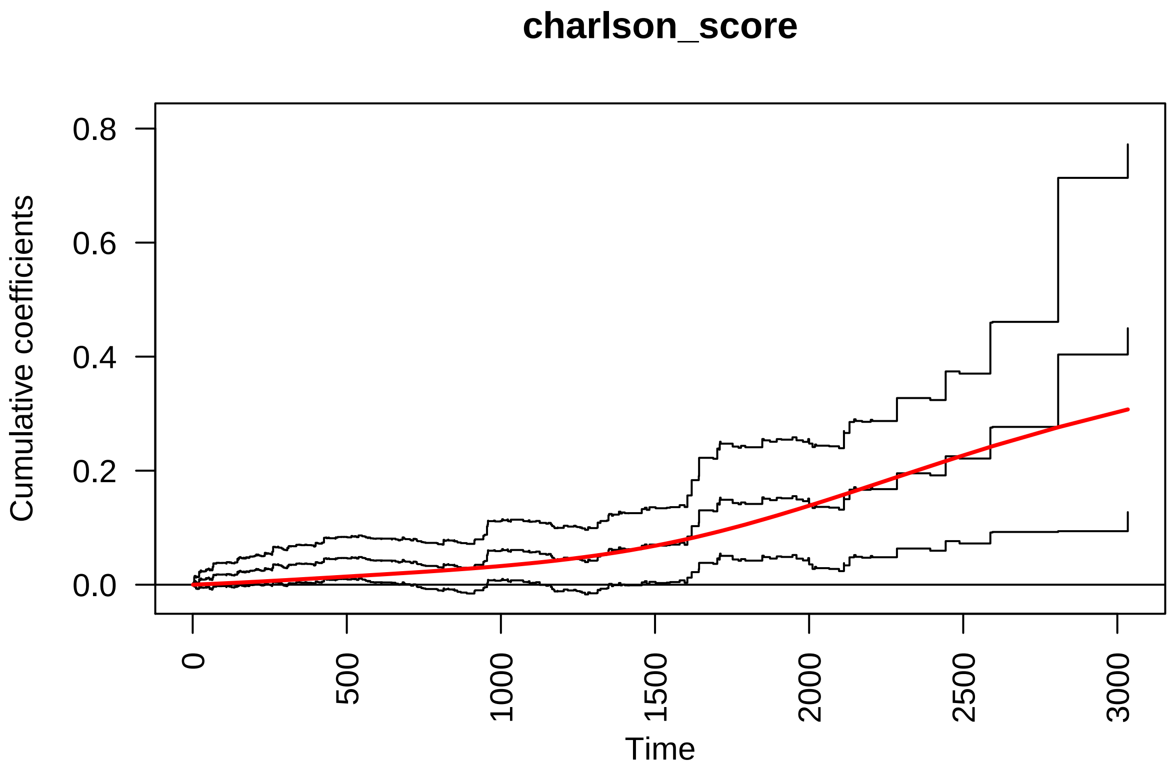
```
##
## Formula:
## ped_status ~ ti(tend, k = 10) + metastases + ti(tend, by = as.ordered(metastases),
##     k = 10, mc = c(1, 0)) + major_complications + ti(tend, by = as.ordered(major_complications),
##     k = 10, mc = c(1, 0)) + age + ti(tend, by = age, k = 10,
##     mc = c(1, 0)) + charlson_score + ti(tend, by = charlson_score,
##     k = 10, mc = c(1, 0)) + sex + transfusion + major_resection
##
## Parametric coefficients:
##                         Estimate Std. Error z value Pr(>|z|)
## (Intercept)            -9.756319   0.384061 -25.403  < 2e-16 ***
## metastasesyes           0.037949   0.123233   0.308 0.758122
## major_complicationsyes  0.702678   0.126452   5.557 2.75e-08 ***
## age                     0.019308   0.005269   3.664 0.000248 ***
## charlson_score          0.128265   0.045268   2.833 0.004604 **
## sexf                    0.195558   0.108301   1.806 0.070967 .
## transfusionyes          0.238512   0.112066   2.128 0.033311 *
## major_resectionyes      0.249730   0.112940   2.211 0.027024 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Approximate significance of smooth terms:
##                                             edf Ref.df Chi.sq  p-value
## ti(tend)                                  3.266  3.960  9.103  0.05775
## ti(tend):as.ordered(metastases)yes        1.003  1.005  9.513  0.00208
## ti(tend):as.ordered(major_complications)yes 5.289  6.165 70.698 5.55e-13
## ti(tend):age                              1.000  1.001  0.068  0.79468
## ti(tend):charlson_score                   2.183  2.682  7.672  0.05013
##
## ti(tend)                                  .
## ti(tend):as.ordered(metastases)yes        **
## ti(tend):as.ordered(major_complications)yes ***
## ti(tend):age
## ti(tend):charlson_score                   .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## R-sq.(adj) =  0.000679   Deviance explained = -10.1%
## fREML = 2.7942e+05  Scale est. = 1         n = 147896
```

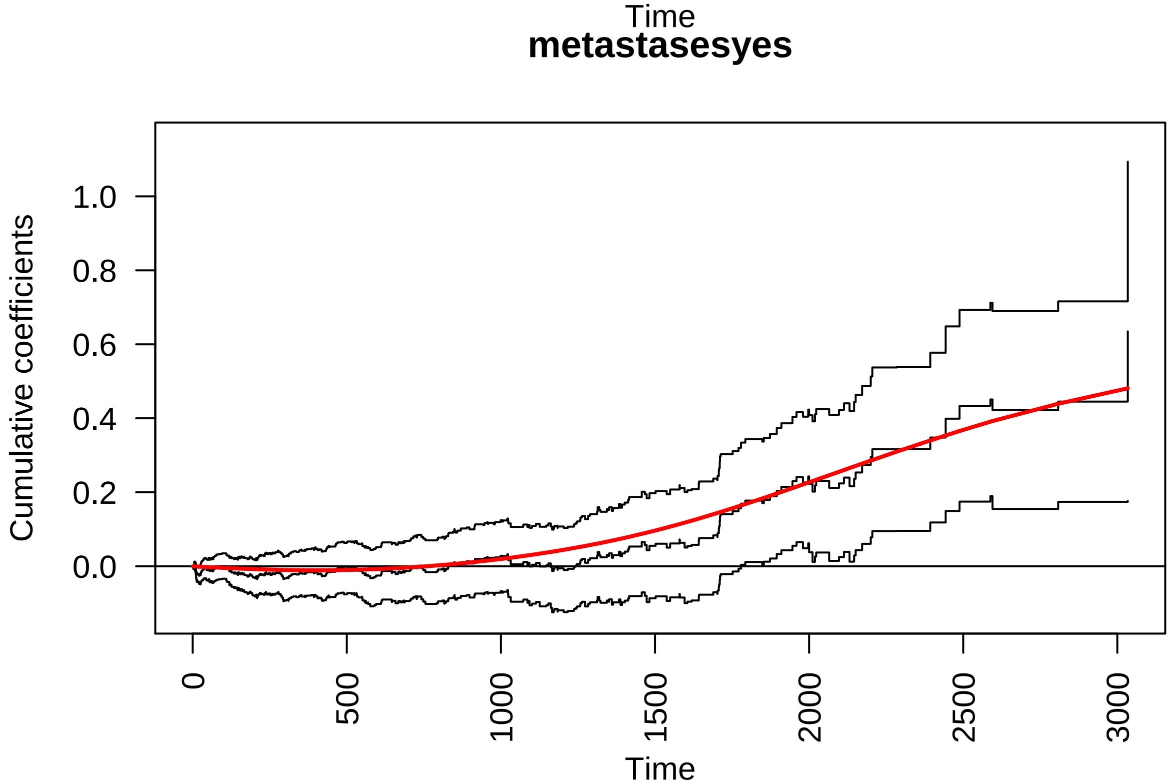
This is the effect estimated for the smooth terms. The total effect of x at time point t is $\beta_x * x + f_x(t)$ where $\beta_x * x$ are the constant effects from the previous graphic and $f_x(t)$ models the effect of the smooth time varying term. Recap the PAM model equation $\lambda_i(t|x_i) = exp(f_0(t_j) + x^T\beta)$ and DISCUSS. They look like that:

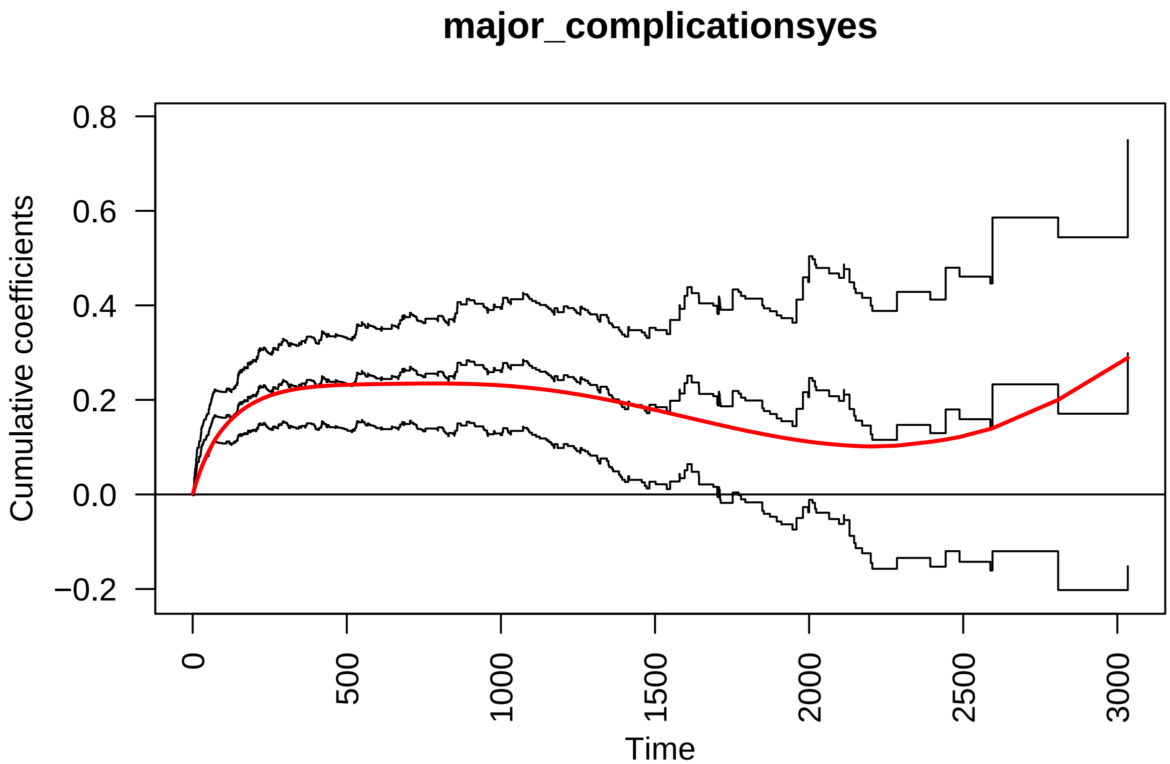


Visual comparison of the time-varying effects from Cox-Aalen model on the cumulated Hazard over time (black) vs. the smooth multiplivative effects of the PAM model (red).




charlson_score
Cumulative coefficients
0.0
0.2
0.4
0.6
0.8
0
500
1000
1500
2000
2500
3000
Time


metastasesyes
Cumulative coefficients
0.0
0.2
0.4
0.6
0.8
1.0
0
500
1000
1500
2000
2500
3000
Time



18 Competing Risk models

- More than one possible event (e.g.: two types of death) next to censoring of which only one can occur. The events **compete** with each other as only one of them can occur.
- Problem with Survival rate estimates (such as KM):
  - Soldiers can die in combat or by accident
  - All 100 soldiers die in helicopter accident at time t **before** they could take part in combat
  - Nobody died in combat at t $\rightarrow S_{Combat}(t) = P(T_{Combat} > t) = 1$ though no combat took place
  - for Kaplan Meier: P(T_{Combat} = t) undefined because nobody at risk at time t.
  - $\Rightarrow$ difficult interpretation of Survival Curves in competing risk scenario
- Approaches:
  - Seperate "cause-specific" Cox models for each type where the competing events are subsumed in censoring.
    * Problem 1: assumption, that $T_1 \perp T_2$
    * Problem 2: Kaplan-Meier Curves are biased
  - Cumulative Incidence Curve as solution to problem 2
  - Discretization: Multinomial GLMs

18.1 Cause-specific Cox PH Models

- One Cox model for each cause.
- Interpretation based on non-occurence of competing events
- Estimate via Partial Likelihood
- Treat competing events $-j$ as being censored which is again the unrealistic independence assumption

$$\lambda_j(t) = \lambda_{0j}(t) exp(X^T \beta_j) \text{ with possibly cause-specific coefficients } \beta_j$$

18.2 Cumulative Incidence Curves

18.2.1 Problem

Study with 100 people over 5 months. Two possible deats: Virus or Cancer. 99 patients die t = 3 on V, 1 dies at t = 5 on C. What is survival rate at t=5 $S(t = 5)$? Depending on the interpretation of V:

1. they represent the C-subpopulation and would have died on Cancer also: $S(t = 5) =$ (1-1)/1 = 0? Thus $Risk_{C1}(T = 5) = 1$ which is the classic Kaplan-Meier way
2. they would have survived Cancer: $S(t = 5) = 1 - 0.01 = 0.99$. Thus $Risk_{C2}(T = 5) = 0.01$ also termed **marginal probability** as V-patients are understood as Cancer-Survivors

We would like to know, who of the V-deaths would have died on Cancer in case they survived V. Which of both Risks is more informative?

18.2.2 Howto CIC

1. Estimate hazard at ordered failure times t_f for event-type j of interest:

$$\hat{\lambda}(t_f)) = \frac{m_{jf}}{n_f} = \frac{\text{\# events j at } t_f}{\text{\# subjects at risk at } st_f}$$

2. Estimate **overall Survival Probability for all event-types** $\hat{S}(t_{f-1})$
3. Compute estimated incidence of failing at time t_f from event type c:

$$\hat{I}_{jf} = \hat{S}(t_{f-1}) \times \hat{\lambda}_j(t_f)$$

4. Cumulate:

Latex does not work for some reason

Kaplan Meier would use event dependent $\hat{S}_c(t_{l-1})$ instead of overall $\hat{S}(t_{l-1})$

18.3 Multinomial time-discret models

Discretize time in q intervals $[a_0, a_1[, ..., [a_{q-1}, a_q[$

$$\lambda_j(t|X) = P(T = t, C = j, T \geq t, X) = \frac{exp(\beta_{0tj} + X^T\beta_j)}{1 + \sum_{i=1}^{k} exp(\beta_{0ti} + X^T\beta_i)} \text{ with \# different events = k + 1}$$

$$\lambda_0(t|X) = P(T > t, C = j, T \geq t, X) = \frac{1}{1 + \sum_{i=1}^{k} exp(\beta_{0ti} + X^T\beta_i)}$$

Interpretation by cause specific log odds w.r.t. reference event type:

$$log\frac{\lambda_j(t|X)}{\lambda_0(t|X)} = \beta_{0tj} + X^T\beta_j$$

and $exp(\beta_l j)$ = the effect of covariate x_l on cause specific hazard w.r.t nothing else happens

19 Random Stuff

19.0.1 Attest significance only based on β and $se(\beta)$

1. compute z-score: $z = \beta/se(\beta)$
2. thresholds for $alpha = 0.05$:
3. one sided: $z_{thresh} = 1.64$
4. two sided: $z_{thresh} = 1.96$
5. Reject H0 (coefficient is not significant) if $z > z_{thresh}$

check their explanation