Additive Hazards

Let $\lambda(t|Z_i)$ be the conditional hazard function given the covariate process

$$Z_i(t) = (Z_{i1}(t), \ldots, Z_{ip}(t))'$$

Then an extraordinarily flexible model is

$$\lambda(t|Z_i) = \alpha(t, Z_i(t)) \quad (1)$$

With α an unknown function of time and the covariates.

- First assume $\alpha(t, 0) = 0$.
- Then take a first order Taylor expanion of $\alpha(t, z)$ about 0

Now it turns out that (1) reduces to

$$\lambda(t|Z_i) = \sum_{j=1}^{p} \alpha_j(t) Z_{ij}(t) \tag{2}$$

This is Aalen's additive hazard model.

Another Form

The previous model is the original formulation. Let's instead use

$$\lambda(t|Z_j(t)) = \beta_0(t) + \sum_{k=1}^{p} \beta_k(t) Z_{jk}(t) \tag{3}$$

to follow the notation in Klein and Moeschberger.

First we make a design matrix $\mathbf{X}(t)$, an $n \times (p+1)$ matrix. For the ith row, set

$$\mathbf{X}_i(t) = Y_i(t)(1, \mathbf{Z}_i(t)).$$

So the ith row of $\mathbf{X}(t)$ is $(1, \mathbf{Z}_i(t))$ if subject i is at risk at time t, otherwise $\mathbf{0}$.

By the form in (3),

$$\mathbf{M}(t) = \mathbf{N}(t) - \int_0^t \mathbf{X}(u)\beta(u)du$$

where $\mathbf{M}(t)$ is a $n \times 1$ vector of martingales. So

$$d\mathbf{N}(t) = \mathbf{X}(t)\beta(t) + d\mathbf{M}(t)$$

Now set $d\mathbf{M}(t) = 0$

$$\int_0^t \beta(u)du = \int_0^t \mathbf{X}^-(u)d\mathbf{N}(u) = \sum_{T_j \le t} \delta_j \mathbf{X}^-(T_j), \quad \text{for } t \le \tau$$

This gives a way to estimate what we need.

Note that $\mathbf{X}^-(u)$ can be any generalized inverse.

We won't estimate $\beta_k(t)$ directly, instead estimate

$$B_k(t) = \int_0^t \beta_k(u)du$$

for each k.

$B_k(t)$ is called a cumulative regression function

Now we will use least-squares.

Let $\mathbf{I}(t)$ be the $n \times 1$ vector with ith element equal to 1 if subject i dies at t and 0 otherwise.

This is essentially $d\mathbf{N}(t)$.

The least squares estimate of $\mathbf{B}(t) = (B_0(t), \ldots, B_p(t))'$ is

$$\widehat{\mathbf{B}}(t) = \sum_{T_i \leq t} \left[\mathbf{X}'(T_i)\mathbf{X}(T_i)\right]^{-1} \mathbf{X}'(T_i)\mathbf{I}(T_i) \tag{4}$$

This is using the generalized inverse suggested by Aalen.

$$
\begin{aligned}
(\widehat{\mathbf{B}} - \mathbf{B})(t) &= \int_0^t \mathbf{X}^-(u) d\mathbf{N}(u) - \int_0^t \beta(u) du \\
&= \int_0^t \mathbf{X}^-(u) \left\{ \mathbf{X}(u)\beta(u) + d\mathbf{M}(u) \right\} - \int_0^t \beta(u) du \\
&= \int_0^t \mathbf{X}^-(u) d\mathbf{M}(u)
\end{aligned}
$$

and so

$$
\begin{aligned}
\langle \widehat{\mathbf{B}} - \mathbf{B} \rangle(t) &= \int_0^t \mathbf{X}^-(u) \langle d\mathbf{M}(u) \rangle \mathbf{X}^-(u)' \\
&= \int_0^t \mathbf{X}^-(u) \mathrm{diag}(\mathbf{Y}(u)\lambda(u)) \mathbf{X}^-(u)'
\end{aligned}
$$

A good estimator for $\mathbf{Y}(t)\lambda(t)$ is $d\mathbf{N}(t)$

So, using $\mathbf{I}(t)$ for $d\mathbf{N}(t)$ and the specific choice of generalized inverse,

$$\widehat{\mathrm{Var}}(\widehat{\mathbf{B}}(t))$$
$$= \sum_{T_i \le t} \left[\mathbf{X}'(T_i)\mathbf{X}(T_i)\right]^{-1} \mathbf{X}'(T_i)\mathrm{D}(\mathbf{I}(T_i))\mathbf{X}(T_i) \left\{\left[\mathbf{X}'(T_i)\mathbf{X}(T_i)\right]^{-1}\right\}'$$

where $D(\mathbf{I}(t))$ is $\mathrm{diag}(\mathbf{I}(t))$.

- $[\mathbf{X}'(T_i)\mathbf{X}(T_i)]^{-1}\mathbf{X}'(T_i)$ is one specific choice for $\mathbf{X}(T_i)^{-}$
- Based on least squares
- Non-optimal
- Optimality requires the true values of parameter functions
- Estimator is defined as long as $\mathbf{X}'(T_i)\mathbf{X}(T_i)$ is invertible

Similar (but not identical) to Aalen's 1989 paper, we will use

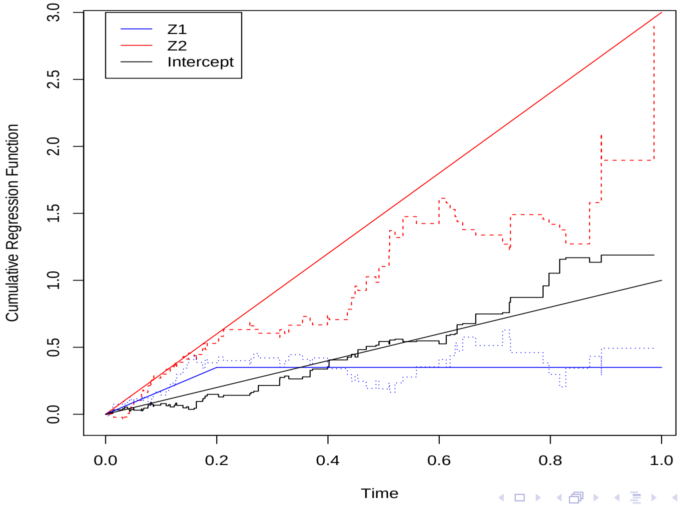
$$\lambda(t) = 1 + 1.75 I\{t \leq 0.2\} Z_1 + 3 Z_2$$

with Z_1, Z_2 binary and

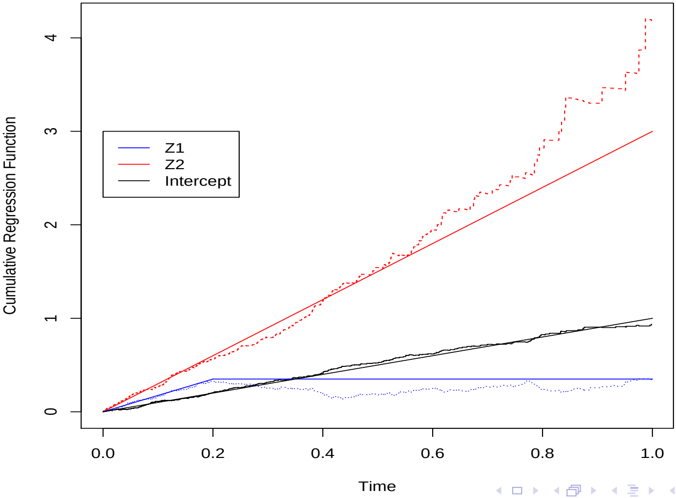
$$P(Z_1 = 0) = P(Z_2 = 0) = 1/2$$

No censoring

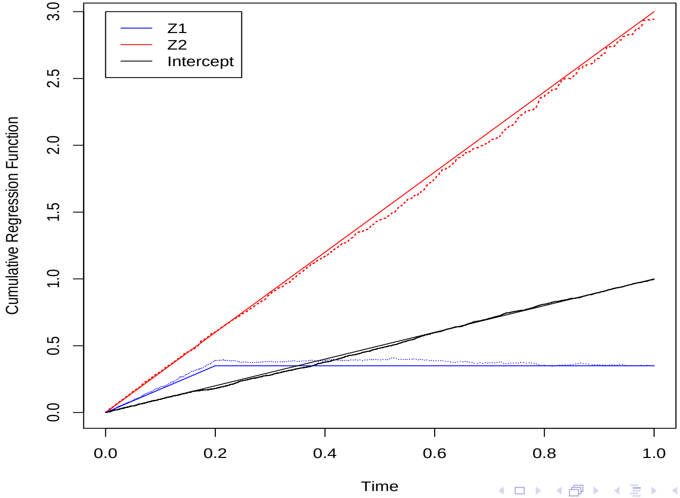
Initial risk set $= 100$



Initial risk set $= 1000$



Initial risk set $= 10000$



Aalen presents the null hypothesis:

$$H_j : \beta_j(t) = 0 \quad \forall t$$

A test statistic for H_j is given by the $(j+1)$th element of

$$\mathbf{U} = \sum_{T_i} \mathbf{K}(T_i)\mathbf{I}(T_i) = \sum_{T_i} \mathbf{W}(T_i)[\mathbf{X}'(T_i)\mathbf{X}(T_i)]^{-1}\mathbf{X}'(T_i)\mathbf{I}(T_i) \tag{5}$$

with

$$\mathbf{W}(t) = \left\{\mathrm{diag}[\mathbf{X}'(t)\mathbf{X}(t)]^{-1}\right\}^{-1}$$

The covariance matrix of $\mathbf{U}$ is

$$\mathbf{V} = \sum_{T_i} \mathbf{K}(T_i)\mathrm{diag}(\mathbf{I}(T_i))\mathbf{K}'(T_i) \tag{6}$$

Then

$$\mathbf{U}'\mathbf{V}\mathbf{U}$$

is asymptotically χ^2_p when H_j holds for all j.

- Based on least squares
- No guarantee estimates are optimal
- No guarantee tests are optimal

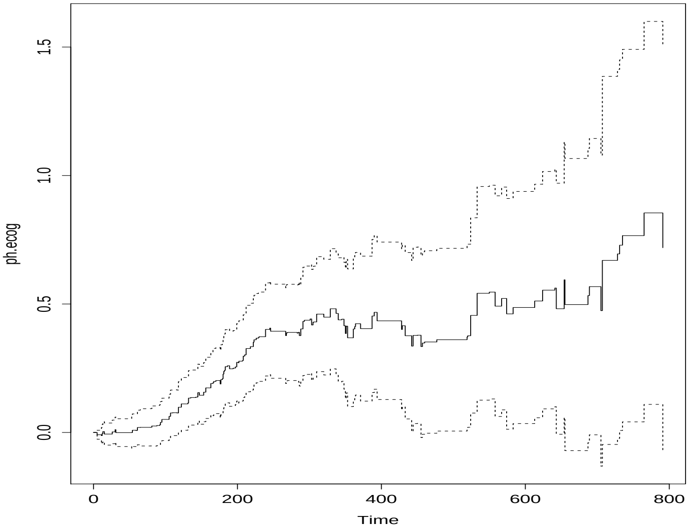
- From survival package in R: Survival in patients with advanced lung cancer from the North Central Cancer Treatment Group.
- Performance scores rate how well the patient can perform usual daily activities.
- We will use ECOG performance score as covariate

Score	ECOG
0	Fully active
1	Restricted activity but ambulatory and capable of light work
2	Ambulatory, capable of self care, no work
3	Limited self care, bed or chair most of the time
4	Completely disabled
5	Dead

```
>library(survival)
>aalen <- aareg(Surv(time, status) ~ age + sex + ph.ecog,
                data=lung)
>aalen
              slope      coef se(coef)      z        p
Intercept  5.05e-03  5.87e-03 4.74e-03  1.240 0.216000
age        4.01e-05  7.15e-05 7.23e-05  0.989 0.323000
sex       -3.16e-03 -4.03e-03 1.22e-03 -3.310 0.000935
ph.ecog    3.01e-03  3.67e-03 1.02e-03  3.610 0.000303

Chisq=26.18 on 3 df, p=8.7e-06; test weights=aalen
```

ECOG Cumulative Regression Function



Lin and Ying's Model

Lin and Ying (1994) present the reduced model

$$\lambda(t|Z_j(t)) = \beta_0(t) + \sum_{k=1}^{p} \beta_k Z_{jk}(t) \tag{7}$$

With the usual definitions, the intensity function for $N_i(t)$ is

$$Y_i(t) d\Lambda(t; Z_i) = Y_i(t)\{d\Lambda_0(t) + \beta_0' Z_i(t) dt\}$$

with $\Lambda_0(t) = \int_0^t \lambda_0(u) du$

Now it's useful to note that $N_i(\cdot)$ can be decomposed into

$$\begin{aligned} N_i(t) =& M_i(t) + \int_0^t Y_i(u) d\Lambda(u; Z_i) \\ =& M_i(t) + \int_0^t Y_i(u) \{ d\Lambda_0(t) + \beta_0' Z_i(t) dt \} \end{aligned} \tag{8}$$

Then the obvious way to estimate $\Lambda_0(t)$ is by

$$\widehat{\Lambda}_0(\widehat{\beta}, t) = \int_0^t \frac{\sum_{i=1}^n \{ dN_i(u) - Y_i(u) \widehat{\beta}' Z_i(u) du \}}{\sum_{j=1}^n Y_j(u)}$$

Use the estimating function

$$U(\beta) = \sum_{i=1}^{n} \int_0^\infty Z_i(t)\{dN_i(t) - Y_i(t)d\widehat{\Lambda}_0(\beta, t) - Y_i(t)\beta' Z_i(t)dt\}$$

Which is equivalent to

$$U(\beta) = \sum_{i=1}^{n} \int_0^\infty \{Z_i(t) - \bar{Z}(t)\}\{dN_i(t) - Y_i(t)\beta' Z_i(t)dt\}$$

where

$$\bar{Z}(t) = \frac{\sum_{j=1}^{n} Y_j(t)Z_j(t)}{\sum_{j=1}^{n} Y_j(t)}$$

Then $U(\beta) = 0$ and solving, we get that

$$\widehat{\beta} = A^{-1} \left[\sum_{i=1}^{n} \int_0^\infty \{Z_i(t) - \bar{Z}(t)\} dN_i(t) \right]$$

with

$$A = \left[\sum_{i=1}^{n} \int_0^\infty Y_i(t) \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} dt \right]$$

The covariance of $\widehat{\beta}$ can be estimated by

$$\left(n^{-1}A\right)^{-1}\left[\frac{1}{n}\sum_{i=1}^{n}\int_0^\infty \{Z_i(t)-\bar{Z}(t)\}^{\otimes 2}dN_i(t)\right]\left(n^{-1}A\right)^{-1}$$

If β_0 is the true covariate vector, then

$$U(\beta_0) = \sum_{i=1}^{n} \int_0^\infty \{Z_i(t) - \bar{Z}(t)\} dM_i(t)$$

and $n^{-1/2} U(\beta_0) \to_d N(0, \Sigma)$, with Σ estimated by

$$n^{-1} \sum_{i=1}^{n} \int_0^\infty \{Z_i(t) - \bar{Z}(t)\}^{\otimes 2} dN_i(t)$$

Asymptotic Considerations

- No guarantee of optimal consistency
- Weighting by true hazard leads to optimality
- Can estimate hazard, then weight

```
library(ahaz)
attach(lung)
time2 <- time[!is.na(ph.ecog) & !is.na(time)]
time2 <- time2 + runif(length(time2), 0, 0.001)
sex2 <- sex[!is.na(ph.ecog) & !is.na(time)]
age2 <- age[!is.na(ph.ecog) & !is.na(time)]
status2 <- status[!is.na(ph.ecog) & !is.na(time)]
ph.ecog2 <- ph.ecog[!is.na(ph.ecog) & !is.na(time)]
ly <- ahaz(Surv(time2, status2),
            cbind(age2,sex2,ph.ecog2))
```

```
Coefficients:
             Estimate Std. Error Z value Pr(>|z|)
age2        2.109e-05  2.149e-05   0.982 0.326304
sex2       -1.216e-03  3.595e-04  -3.384 0.000715 ***
ph.ecog2    1.116e-03  3.039e-04   3.672 0.000240 ***
```