für Weibull:

$h(t) = \alpha\lambda x^{\alpha-1}$ $\quad S(t) = \exp(-\lambda x^{\alpha})$ $\quad f(t) = \alpha\lambda x^{\alpha-1} \exp(-\lambda x^{\alpha})$

für Expo:

$h(t) = \lambda$ $\quad S(t) = \exp(-\lambda x)$ $\quad f(t) = \lambda \exp(-\lambda x)$

$$S(t) = \exp\left[-\int^{t} h(u)\,du\right.$$

$$h(t) = -\frac{dS(t)/dt}{S(t)}$$

$$\ln(-\ln\hat{S}) = \ln H$$

FPM

PH:

$$g(S(t;z)) = g(S_0(t)) + \beta^T Z$$

→ model $g(S_0(t))$ mit Spline, $g(x;\vartheta) = \ln \frac{x^{-\vartheta}-1}{\vartheta}$

für $\vartheta \to 0$: $\lim_{\vartheta\to 0} g(x;\vartheta) = \log(-\log(x))$

<u>bei Weibull:</u> $\ln H(t) = \ln(-\ln\hat{S}(t)) = \ln(\lambda t^{a}) = \ln(\lambda) + \alpha\ln(t)$

$= \ln(\lambda) + \alpha x$ für $x = \ln(t)$

$= \gamma_0 + \gamma_1 x \quad$ mit $\gamma_0 = \ln(\lambda)$; $\alpha = \gamma_1$

$\to$ linear in $\ln(t)$

sei Expo: $\ln H(t) = \ln(-\ln S(t)) = \ln(\lambda t) = \ln(\lambda) + \ln(t)$

$= \ln(\lambda) + x$

We smooth

$$g(S(t;Z)) = \ln(-\ln S(t;Z)) = \ln H_0(t) + \beta^T Z = s(x;\gamma) + \beta^T Z$$

$s(x;\gamma) = \gamma_0 + \gamma_1 x + \gamma_2 v_1(x) + \ldots + \gamma_{m+1} v_m(x)$ is ncs.

Weibull für $m=0$.

mit m knots $k_{min}, k_1, \ldots, k_m, k_{max}$. Each $m+1$ function depends on interval not except $m=1$

j^{th} basic function defined for $j = 1, \ldots, m$ as

$$v_j(x) = (x - k_j)_+^3 - \lambda_j (x - k_{min})_+^3 - (1 - \lambda_j)(x - k_{max})_+^3$$

mit $\lambda_j = (k_{max} - k_j)/(k_{max} - k_{min})$; $df = m+1$

PH: $g(S(t;Z)) = \ln H(t;Z) = s(x;\gamma) + \beta^T \mathbf{z} = g(S_0(t)) + \beta^T \mathbf{z}$

mit $S_0(t) = S(t;0)$

$\neg$PH:

$$= \gamma_0 + \gamma^T \mathbf{v}(x) + \beta^T \mathbf{z}$$

mit $\mathbf{v}(x) = (x, v_1(x), \ldots, v_m(x))^T$

(Lalin: B-splines)
(Shao: linear splines)

if first k covariates in set $\mathbf{z}$ are non-PH:

$$\gamma_j = \gamma_{j0} + \sum_{l=1}^{k} \gamma_{jl} z_l$$

See Appendix B

$g(S_0(t))$ smoothed in $\ln(t)$ $\to$ not necessarily monoton! But practically given if $n \gg 0$

R+P 2002

PH in Cox: $h(t;\mathbf{z}) = h_0(t)\exp(\boldsymbol{\beta}^T\mathbf{z})$ mit $h_0(t) = h(t;0)$

$$H(t;\mathbf{z}) = H_0(t)\exp(\boldsymbol{\beta}^T\mathbf{z})$$

$s \equiv s(x;\gamma) \to \ln H(t;\mathbf{z}) = s(x;\gamma) + \boldsymbol{\beta}^T\mathbf{z}$

eg $df = 4$: at 25%, 50%, 75% in $\ln(t)$

extreme knots at extreme uncensored survival times

Cox time dependent: $\log HR = \beta_1 z_1 [1 + \beta_1^x f(t)]$ für var z_1

$\to$ time-varying regression coefficient $\beta_1(t) = \beta_1 [1 + \beta_1^x f(t)]$

β_1^x estimated in Cox-model with fixed z_1 and t-dependent covariate $f(t) z_1$

time-dependent splines

PH mit $m=1$, eine covariate:

$\ln H(t;z_1) = \gamma_0 + \gamma_{10}x + \gamma_{20}v_1(x) + \beta_1 z_1$. $\log HR = \beta_1 z_1$, $\perp\!\!\!\perp t$

$\log CHR = \beta_1 z_1$, $''$ t ← warum ?

time-d:

more general: $= \gamma_0 + (\gamma_{10} + \gamma_{11} z_1)x + (\gamma_{20} + \gamma_{21} z_1)v_1(x) + \beta_1 z_1$

mit log CHR for z_1

(

sei $x = f(t) = \ln t$; $\gamma_{11} = \beta_1^x$; $\gamma_{21} = 0$:

$$\ln H(t;z_1) = \gamma_0 + \gamma_{10}x + \beta_1^x z_1 x + \gamma_{20}v_1(x) + \beta_1 z_1$$

$$= \gamma_0 + \gamma_{10}x + \gamma_{20}v_1(x) + \beta_1 z_1 + z_1 \beta_1^x f(t)$$

)

$$\log CHR = \ln H(t;z_1) - \ln H(t;0)$$
$$= \gamma_0 + (\gamma_{10} + \gamma_{11} z_1)x + (\gamma_{20} + \gamma_{21} z_1) v_1(x) + \beta_1 z_1$$
$$- [\gamma_0 + \gamma_{10} x + \gamma_{20} v_1(x)]$$
$$= \gamma_{11} z_1 x + \gamma_{21} z_1 v(x) + \beta_1 z_1 = z_1 (\gamma_{11} x + \beta_1 + \gamma_{21} v(x))$$

$\rightarrow$ multiply with ncs in $x = \ln t$

$$\ln H(t;\mathbf{z}) = \gamma_0 + \boldsymbol{\gamma}^T \mathbf{v}(x) + \boldsymbol{\beta}^T \mathbf{z}$$

mit $\mathbf{v}(x) = (x, v_1(x), \dots, v_m(x))^T$, $\dim(\boldsymbol{\gamma}) = m+1$,

$j = 1, \dots, m+1$:

$$\gamma_j = \begin{cases} \gamma_{j0} & \text{for } \dim(z) = 0 \hat{=} PH \\ \gamma_{j0} + \sum_{l=1} \gamma_{jl} z_l & \text{for } \dim(z) > 0 \end{cases}$$

e.g. time varying $\log CHR$ at fixed z except z_1:

$$\ln H(t; z_1, z_2, \dots) - \ln H(t; 0, z_2, \dots)$$
$$= z_1 [\beta_1 + \gamma_{11} x + \gamma_{21} v_1(x) + \dots + \gamma_{m+1,1} v_m(x)]$$

RP 2011

$$\ln H(t;\mathbf{x}) = \ln H_0(t) + \mathbf{x}'\beta = s(\ln t) + \mathbf{x}'\beta$$

rstpm2

- simple gude:

PH: $S(t|\mathbf{x}) = \exp\left[-\exp\left(s(\ln t;\gamma) + \sum_j \beta_j x_j\right)\right]$

x_j: covariates

$$H(t|\mathbf{x}) = -\log S(t|\mathbf{x}) = \exp\left(s(\log t;\gamma) + \sum_j \beta_j x_j\right)$$

$$h(t|\mathbf{x}) = \frac{d}{dt} H(t|\mathbf{x}) = \exp\left(s(\log t;\gamma) + \sum_j \beta_j x_j\right) \times \frac{ds(\log(t);\gamma)}{dt}$$

sei 2 sets of covariates:

$$\mathbf{x}_1 = (x_{1j}) \; ; \; \mathbf{x}_2 = (x_{2j})$$

dann ist

$$HR = \exp\left(\sum_j \beta_j (x_{2j} - x_{1j})\right) = \exp(\beta_j) \text{ if all other } x \text{ equal,}$$

and $x_{2j} = x_{1j} + 1$

in case of PH:

$$h(t|\mathbf{x}) = \exp\left(\gamma_0 + \sum_j \beta_j x_j\right) \text{ mit } \log h_0(t) = \gamma_0$$

$$S(t|\mathbf{x}) = \exp\left(-\exp\left(\gamma_0 + \log t + \sum_j \beta_j x_j\right)\right)$$

package default:

$$s(\log t;\gamma) = \sum_{k=1}^{K} B_k(\log t)\gamma_k$$

wobei $B_K(\log t)$ is natural spline. $df = K$

benutzt splines::ns

package function

tvc = list(hormon=3) $\hat{=}$ smooth.formula = ~ ... + hormon:nsx(log(time), df=3)

$$v_j(x) = (x-k_j)_+^3 - \frac{k_{max}-k_j}{k_{max}-k_{min}}(x-k_{min})_+^3 - \left(1-\frac{k_{max}-k_j}{k_{max}-k_{min}}\right)(x-k_{max})_+^3$$

j = 1:

$$v_1(x) = (\underbrace{x-k_1}_{0 \text{ if } x \le k_1})_+^3 - \frac{k_{max}-k_1}{k_{max}-k_{min}}(\underbrace{x-k_{min}}_{0 \text{ if } x<k_{min}})_+^3 - \left(1-\frac{k_{max}-k_1}{k_{max}-k_{min}}\right)(\underbrace{x-k_{max}}_{0 \text{ if } x<k_{max}})_+^3$$

$x \le k_{min}$: $0 - 0 - 0 = 0$

$k_{min} < x < k_1$: $-\frac{k_{max}-k_1}{k_{max}-k_{min}}(x-k_{min})^3$

$k_{min} < k_1 < x$: $(x-k_1)^3 - \frac{k_{max}-k_1}{k_{max}-k_{min}}(x-k_{min})^3$

$j=1,\ x=k_1$: $-\frac{k_{max}-k_1}{k_{max}-k_{min}}(k_1-k_{min})^3$

=

$$s(x) = \beta_{00} + \beta_{10}x + \sum_{j=1}^{m} \beta_j[(x-k_j)_+^3 - \lambda_j(x-k_{\min})_+^3 - (1-\lambda_j)(x-k_{\max})_+^3]$$

$$= \gamma_0 + \gamma_1 x + \gamma_2 v_1(x) + \cdots + \gamma_{m+1} v_m(x)$$

where $\gamma_0 = \beta_{00}$, $\gamma_1 = \beta_{10}$ and for $j = 1, \ldots, m$

$$\gamma_{j+1} = \beta_j$$
$$v_j(x) = (x-k_j)_+^3 - \lambda_j(x-k_{\min})_+^3 - (1-\lambda_j)(x-k_{\max})_+^3$$

sei $m = 2$.

$$s(x) = \beta_{00} + \beta_{10}x + \beta_1\left[(x-k_1)_+^3 - \lambda_1(x-k_{min})^3 - (1-\lambda_1)(x-k_{max})_+^3\right]$$

$$s(x < k_{min}) = \beta_{00} + \beta_{10}$$

$$s(k_{min} < x\, k_1 < k_{max}) = \beta_{00} + \beta_{10}x +$$

Annahme: proportional hazards, expo survival

sei α Proportionalitätsfaktor: $\alpha = \frac{\lambda_1}{\lambda_0}$

$$\exp(-\lambda_0 \alpha t) = \exp(-\lambda_1 t)$$

$$\int_0^\tau \exp(-\lambda_0 \alpha t)\,dt = \int_0^\tau \exp(-\lambda_1 t)\,dt$$

$$= -\frac{\exp(-\lambda_0 \alpha \tau)}{\alpha \lambda_0} + \frac{\exp(-\lambda_0 \alpha 0)}{\alpha \lambda_0}$$

$$= \frac{1-\exp(-\lambda_0 \alpha \tau)}{\alpha \lambda_0}$$

$$= \frac{1-\exp(-\lambda_0 \alpha \tau)}{\alpha \lambda_0} \cdot \frac{1-\exp(-\lambda_0 \tau)}{\lambda_0} \cdot \frac{\lambda_0}{1-\exp(-\lambda_0 \tau)}$$

$$= \frac{1-\exp(-\lambda_0 \alpha \tau)}{\alpha \cancel{\lambda_0}} \cdot \int_0^\tau \exp(-\lambda_0 t)\,dt \cdot \frac{\cancel{\lambda_0}}{1-\exp(-\lambda_0 \tau)}$$

$$= \frac{1-\exp(-\lambda \alpha \tau)}{\alpha(1-\exp(-\lambda_0 \tau))} \int_0^\tau \exp(-\lambda_0 t)\,dt$$

$$\rightarrow (1) \int_0^\tau \exp(-\lambda_1 t)\,dt = \frac{1-\exp(-\lambda_0 \alpha \tau)}{\alpha(1-\exp(-\lambda_0 \tau))} \int_0^\tau \exp(-\lambda_0 t)\,dt$$

$$\frac{\int_0^\tau \exp(-\lambda_1 t)\,dt}{\int_0^\tau \exp(-\lambda_0 t)\,dt} = \frac{1-\exp(-\lambda_1 \tau)}{\frac{\lambda_1}{\lambda_0}\left(1-\exp(-\lambda_0 \tau)\right)}$$

$$= \frac{\lambda_0 \left(1-\exp(\lambda_1 \tau)\right)}{\lambda_1 \left(1-\exp(-\lambda_0 \tau)\right)} = \text{RMST-Ratio}$$

für $\alpha = \frac{\lambda_1}{\lambda_0}$:

$$\text{RMST-Ratio} = \frac{1-\exp(\alpha \lambda_0 \tau)}{\alpha\left[1-\exp(-\lambda_0 \tau)\right]}$$

$$\int_0^\tau \exp(\lambda_1 t)\,dt = \frac{1-\exp(-\lambda_0 \alpha \tau)}{\alpha \lambda_0}$$

$$\int_0^\tau \exp(\lambda_1 t)\,dt - \int_0^\tau \exp(\lambda_0 t)\,dt = \frac{1-\exp(-\lambda_1 \tau)}{\lambda_1} - \frac{1-\exp(-\lambda_0 \tau)}{\lambda_0}$$

$$\text{RMST-Diff} = \frac{\left[1-\exp(-\lambda_1 \tau)\right]\lambda_0 - \left[1-\exp(-\lambda_0 \tau)\right]\lambda_1}{}$$

$$\lambda_1\lambda_0 \qquad\qquad \lambda_1\lambda_0$$

$$= \frac{\lambda_0 + \lambda_1\exp(-\lambda_0\tau) - \lambda_0\exp(-\lambda_1\tau) - \lambda_1}{\lambda_1\lambda_0}$$

$$\text{für } \alpha = \frac{\lambda_1}{\lambda_0}: \quad = \frac{\lambda_0 + \alpha\lambda_0\exp(-\lambda_0\tau) - \lambda_0\exp(-\alpha\lambda_0\tau) - \alpha\lambda_0}{\alpha\lambda_0^2}$$

$$= \frac{\cancel{\lambda_0}\left(1 + \alpha\exp(-\lambda_0\tau) - \exp(-\alpha\lambda_0\tau) - \alpha\right)}{\alpha\lambda_0^{\cancel{2}}}$$

$$= \frac{1 + \alpha\exp(-\lambda_0\tau) - \exp(-\alpha\lambda_0\tau) - \alpha}{\alpha\lambda_0}$$

Zusammenfassung

Unter Annahme von proportional hazard und Proportionalitätsfaktor $\alpha = \frac{\lambda_1}{\lambda_0}$ besteht für exponential Survival der folgende Zusammenhang:

$$\text{RMST-Difference} = \frac{1 + \alpha\exp(-\lambda_0\tau) - \exp(-\alpha\lambda_0\tau) - \alpha}{\alpha\lambda_0} = \int_0^\tau S(t,\lambda_1)\,dt - \int_0^\tau S(t,\lambda_0)\,dt$$

$$\text{RMST-Ratio} = \frac{1 - \exp(\alpha\lambda_0\tau)}{\alpha\left[1 - \exp(-\lambda_0\tau)\right]} = \frac{\int_0^\tau S(t,\lambda_1)\,dt}{\int_0^\tau S(t,\lambda_0)\,dt}$$