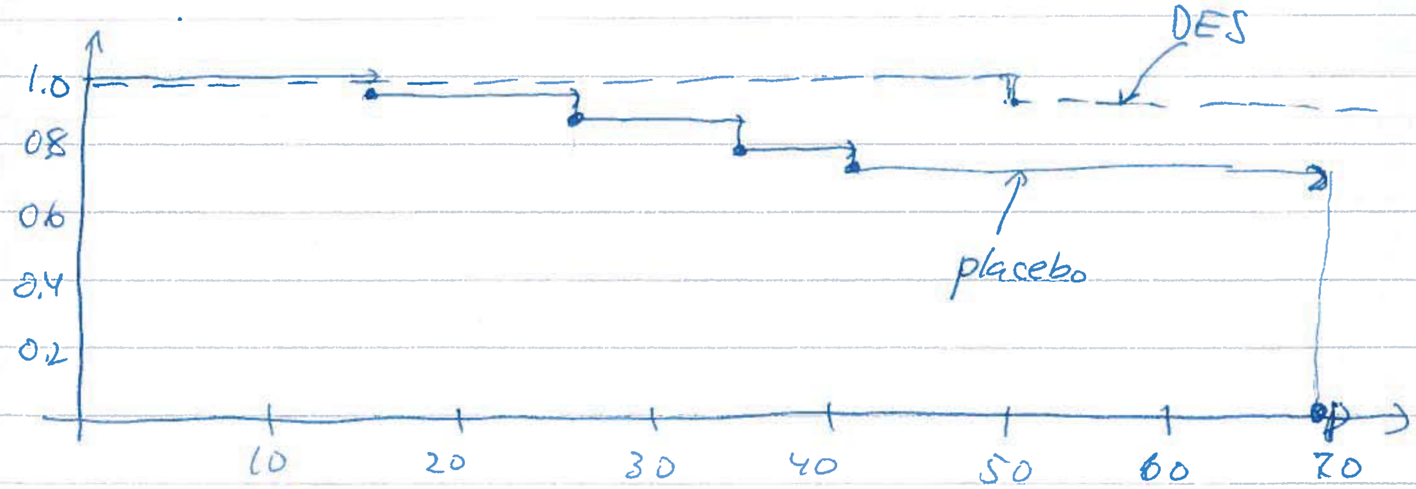
SOLUTION STK 4080 Autumn 2019

PROBLEM 1.

a) $\hat{S}(t) = \prod_{T_i \le t} \left(1 - \frac{1}{Y(T_i)}\right)$

	t	$Y(t)$	$\left(1 - \frac{1}{Y(t)}\right)$	$\hat{S}(t)$
Treat =0	14	17	$\left(1 - \frac{1}{17}\right)$	0,9412
	26	14	$\left(1 - \frac{1}{14}\right)$	0,8739
	36	13	$\left(1 - \frac{1}{13}\right)$	0,8067
	42	12	$\left(1 - \frac{1}{12}\right)$	0,7395
	69	1	$(1 - 1)$	0
Treat =1	50	16	$\left(1 - \frac{1}{16}\right)$	0,9375



Estimated median: 69. (placebo)

No estim. median for DES, because the estimated survival does not reach 0.5.

Restricted mean up to $t=60$: Placebo: $14 \cdot 1 + 12 \cdot 0.9412 + \dots + 18 \cdot 0.7395 = 52.18$

Restr. mean DES : $50 + 10 \cdot 0.9375 = \underline{59.375}$

b) Cox-model is

$$\alpha(t\,;\,\text{Treat}) = \alpha_0(t)\, e^{\beta \cdot \text{Treat}}$$

The p-values are from 0.03 to 0.07 which shows a slightly significant case. It should be noted, however that asymptotics may not be valid because of very few observed events.

Estimated hazard ratio is

$$e^{\hat\beta} = 0.1384$$

a 95% C.I. is obtained for β by

$$-1.9780 \pm 1.96 \cdot 1.0982$$

$$(-4.1304,\ 0.1744)$$

By exponentiation we get the 95% CI for e^{β}:

$$\underline{(0.016,\ 1.1906)}$$

c) The model is a Cox-model with fixed covariates, and hazard given as

$$\alpha(t;\underset{\sim}{x}) = \alpha_0(t)\cdot e^{\beta_1 \cdot TREAT + \beta_2 Age + \beta_3 Shb + \beta_4 Size + \beta_5 Index}$$

Following the signs of the estimated β_i, it seems that

hazard $\downarrow$ if TREAT = 1
hazard $\uparrow$ with age
hazard $\downarrow$ with increasing Shb
" $\uparrow$ with increasing size of tumor
$\uparrow$ " " Index

Except possibly Shb, these directions seem sensible. However, several coefficients are not significantly different from 0.
Only "Index" is significant at 5% level.

It is noticeable that the p-value of Treat is now 0.3287, so Treat seems to be far from significant.
This is apparently a different conclusion than in b) and may be because the other covariates differ between the two groups in a way making a dependency between group and covariates.

Problem 2

a) $N(0) = 0$, $N(t)$ is non-decreasing ($\equiv$ increasing), $N(t)$ is right continuous, $N(t)$ makes jumps of size 1, $N(t)$ is measurable w.r.t. $\mathcal{F}_t$.

$\Lambda(t)$ is increasing and predictable.

$M(t)$ is a martingale means that

$$E[M(t|\mathcal{F}_s)] = M(s) \quad \text{for all } 0 \le s < t.$$

$$M(0) = 0.$$

b) $$\langle M \rangle (t) = \int_0^t Var(dM(s) \,|\, \mathcal{F}_{s-})$$

Since $E(M(t)) = 0$ we have

$$Var(M(t)) = E(M(t)^2) \underset{\text{by (i)}}{=} E(\langle M \rangle (t))$$

$$\underset{\text{by (ii)}}{=} E(\Lambda(t))$$

c) Must show that

$$E(N(t) - A(t) \,|\, \mathcal{F}_s) = N(s) - A(s) \quad \text{when } 0 \le s < t$$

Now $E(N(t)-A(t) \mid \mathcal{F}_s)$

$$= E(N(t)-N(s)+N(s)-A(t) \mid \mathcal{F}_s)$$

$$= \underbrace{E(N(t)-N(s) \mid \mathcal{F}_s)}_{\text{independ. by (II)}} + N(s)-A(t)$$

$$\underset{\text{by (I)}}{=} A(t)-A(s)+N(s)-A(t) = N(s)-A(s).$$

Q.E.D

Problem 2.

a) For the ith process, the rate $\alpha(t;\underset{\sim}{\theta})$ is in force throughout the interval $[0,\tau_i]$. Thus the intensity is $\lambda_i(t) = I(t \le \tau_i)\alpha(t;\underset{\sim}{\theta})$ and the ith process jumps at $T_{i1}, \dots, T_{iN_i}$. Thus the first part $\{\}$ of $L(\underset{\sim}{\theta})$, for the ith individual, will be

$$\prod_{0<t\le\tau} \lambda_i(t;\underset{\sim}{\theta})^{\Delta N_i(t)} = \prod_{k=1}^{N_i(\tau_i)} \alpha(T_{ik};\underset{\sim}{\theta})$$

Note then that

$$e^{-\int_0^{\tau} \lambda_\cdot(t;\underset{\sim}{\theta})dt} = \prod_{i=1}^{n} e^{-\int_0^{\tau_i} \alpha(t;\underset{\sim}{\theta})dt}$$

which gives (3)

b) $\alpha(t;a,b) = abt^{b-1}$; $A(t;a,b) = \int_0^t \alpha(t;a,b)\,dt = at^b$

Then (3) becomes

$$L(a,b) = \prod_{i=1}^{n} \left\{ \left(\prod_{k=1}^{N_i(\tau_i)} ab\, T_{ik}^{\,b-1} \right) e^{-\int_0^{\tau_i} abt^{b-1}dt} \right.$$

$$= a^N b^N \prod_{i=1}^{n} \prod_{k=1}^{N_i(\tau_i)} T_{ik}^{\,b-1}\, e^{-a\tau_i^b}$$

Taking the log gives the log-likelihood displayed in the exercise.

$$U_1(a,b) = \frac{\partial}{\partial a} l(a,b) = \frac{N}{a} - \sum_{i=1}^{n} \tau_i^b$$

$$U_2(a,b) = \frac{\partial}{\partial b} l(a,b) = \frac{N}{b} + S' - a \sum_{i=1}^{n} \tau_i^b \log(\tau_i)$$

Suppose $\tau_i \equiv \tau$. Then we get the equations

(1) $\frac{N}{a} - n\tau^b = 0$

(2) $\frac{N}{b} + S' - \cancel{a}n\tau^b \log\tau = 0$

(1) $\Rightarrow$ $n\tau^b = \frac{N}{a}$. Substituting this in (2) gives

(2)' $\frac{N}{b} + S - \cancel{a}\frac{N}{\cancel{a}} \log\tau = 0$

$$\Rightarrow \quad \frac{N}{b} = N \log \tau - S$$

$$\Rightarrow \quad \hat{b} = \frac{N}{N \log \tau - S}$$

$$\hat{a} = \frac{N}{n \tau^{\hat{b}}}$$

c) Must calculate

$$\frac{\partial^2 \ell}{\partial a^2} = -\frac{N}{a^2}, \quad \frac{\partial^2 \ell}{\partial a \partial b} = -\sum_{i=1}^{n} \tau_i^{b} \log \tau_i$$

$$\frac{\partial^2 \ell}{\partial b^2} = -\frac{N}{b^2} - a \sum_{i=1}^{n} \tau_i^{b} (\log \tau_i)^2$$

Thus

$$I(\theta) = \begin{bmatrix} \frac{N}{a^2} & \sum \tau_i^{b} \log \tau_i \\ \sum \tau_i^{b} \log \tau_i & \frac{N}{b^2} + a \sum_{i=1}^{n} \tau_i^{b} (\log \tau_i)^2 \end{bmatrix}$$

Expected ~~value~~ information: Replace the N by $E(N) = a \sum_{i=1}^{n} \tau_i^{b}$

Diagonal entries of $I(\theta)^{-1}$ (and the expected) are estimates of $Var(\hat{a})$ and $Var(\hat{b})$ when ~~t~~ ML-estimates are substituted for a, b.

d) Shared frailty models assume that there might be unobserved differences between the equipment that can be taken into account in a formal way. <u>Within</u> observations from the same equipment, the frailty will be assumed to be the same

The contribution from the ith process is

by (3), $\left\{ \prod_{k=1}^{N_i(\tau_i)} Z_i \cdot \alpha(T_{ik};\theta) \right\} e^{-Z_i \cdot \tau_i^{b}}$

$$= \left\{ \prod_{k=1}^{N_i(\tau_i)} \alpha(T_{ik};\theta) \right\} \cdot Z_i^{N_i(\tau_i)} e^{-Z_i \tau_i^{b}}$$

(conditionally given Z_i).

The unconditional contribution is the expected value of this with respect to the distribution of Z_i, i.e.

$$\left(\prod_{k=1}^{N_i(\tau_i)} \alpha(T_{ik};\theta) \right) E_{Z_i}\left[Z^{N_i(\tau_i)} e^{-Z \tau_i^{b}} \right]$$

$$= \left\{ \prod_{i=1}^{N_i(\tau_i)} \alpha(T_{ik};\theta) \right\} \cdot \cancel{\mathcal{LL}} (-1)^{N_i(\tau_i)} \mathcal{L}^{(N_i(\tau_i))}(\tau_i^{b}$$

PROBLEM 4

a) $Z_1(t) = N_1(t) - \int_0^t \frac{Y_1(t)}{Y_0(t)} \, dN_0(t)$

By hint we also have

$$dN_0(t) = Y_0(t)\alpha(t)dt + dM_0(t)$$

so

$$Z_1(t) = \int_0^t Y_1(t)\alpha(t)dt + M_1(t)$$
$$- \int_0^t \frac{Y_1(t)}{Y_0(t)} \left[Y_0(t)\alpha(t)dt + dM_0(t) \right]$$
$$= M_1(t) - \int_0^t \frac{Y_1(t)}{Y_0(t)} \, dM_0(t)$$

which is a martingale since the last term is a stochastic integral of a martingale.

b) By hint in a) we can write

$$\langle Z_1 \rangle(t) = \int_0^t \frac{Y_1(s)Y_2(s)}{Y_0(s)^2} Y_0(s)\alpha(s)ds$$

$$= \int_0^t \frac{Y_1(s)Y_2(s)}{Y_0(s)^2} dN_0(s) - \int_0^t \frac{Y_1(s)Y_2(s)}{Y_0(s)^2} dM_0(s)$$

Taking expectations, we get

$$E\,Var(Z_1(t)) = E\langle Z_1 \rangle(t) = E \int_0^t \frac{Y_1(s)Y_2(s)}{Y_0(s)^2} dN_0(s)$$

Hence $X^2(t_0) = \dfrac{Z_1(t_0)^2}{Var(t_0)}$

which standardizes the $Z_1(t_0)$.
It follows from the theory that this is asymptotically χ^2_1.

c) By (4) we have

$$O_1 = N_1(t_0) = 5$$
$$O_2 = N_2(t_0) = 1$$
$$E_1 = \int_0^{t_0} \frac{Y_1(t)}{Y_1(t)+Y_2(t)}\, dN_\bullet(t)$$

= a sum which increases by $\dfrac{Y_1(T_j)}{Y_1(T_j)+Y_2(T_j)}$ at each event time for the process $N_\bullet(t)$:

$$= \underset{T_j=14}{\frac{17}{17+19}} + \underset{T_j=26}{\frac{14}{14+18}} + \underset{T_j=36}{\frac{13}{13+17}} + \underset{T_j=42}{\frac{12}{12+17}} + \underset{T_j=50}{\frac{10}{10+6}} + \underset{T_j=69}{\frac{1}{1+2}}$$

$= 2.475$

Likewise we get for $V_{11}(t_0)$ from (5):

$$\frac{17\cdot 19}{36^2} + \frac{14\cdot 18}{32^2} + \frac{13\cdot 17}{30^2} + \frac{12\cdot 17}{29^2} + \frac{10\cdot 16}{26^2} + \frac{1\cdot 2}{3^2}$$

$$= 1.44\cancel{2388}$$

Hence $X^2(t_0) = \dfrac{2.525^2}{1.442} = \underline{4.42}$

which is > 3.84 and leads to rejection of H_0 at 5% level. (But asymptotics may not be accurate.)

Next we have $O_1 - E_1 = 5 - 2.475 = 2.525$

so $O_2 - E_2 = 1 - \cancel{3}\,3.525 = -2.525$

Thus $\dfrac{(O_1-E_1)^2}{E_1} + \dfrac{(O_2-E_2)^2}{E_2} \cancel{= 4.38}$

$$= \frac{(5-2.475)^2}{2.475} + \frac{(1-3.525)^2}{3.525} = 4.38$$

(which is slightly smaller than $X^2(t_0)$).