Survival analysis

1 Selection phenomena

Opgave 1.1 (Frailty-model**)**

Assume that the survival time T has the conditional hazard function

$$\lambda(t|A,Z) = Z\lambda_0(t)e^{\beta A}\exp\{\theta\Lambda_0(t)e^{\beta A}\}$$

given A and Z, where A is binary (treatment indicator, $A = 1$ corresponds to active treatment). The so-called frailty variable Z is unobserved and assumed to be Gamma distributed with mean 1 and variance θ. It also assumed that $\lambda_0(t)$ is hazard function and that $\Lambda_0(t) = \int_0^t \lambda_0(s)\,ds$. The term "frailty" stems from the fact that the larger Z the larger $\lambda(t|A,Z)$ (ie more frail). We also assume that A and Z are independent, which will be the case if treatment is randomized.

(a) Derive the observed hazard function, that is, $\lambda(t|A)$, and show that

$$\frac{\lambda(t|A=1)}{\lambda(t|A=0)} = \exp(\beta) \tag{1}$$

The model in (1) is called a Cox-model (proportional hazards). Assume in the following that $\beta < 0$ (beneficial treatment effect).

(b) Show that

$$\frac{E(Z|T>t, A=1)}{E(Z|T>t, A=0)} = \exp\{\Lambda_0(t)(1-e^{\beta})\}$$

(c) Use the result in (b) to conclude about the individuals in the two treatment groups concerning whether they are equally "frail" as time passes by. Start with considering $t = 0$.

2 Nelson-Aalen estimator

Opgave 2.1 (Two-sample situation)

Assume that we have observations from two groups of patients (two different treatments). Hence, we assume that we have independent observations (T_{1i}, Δ_{1i}) (group 1) and (T_{2i}, Δ_{2i}) (group 2) with n_1 observations from group 1 and n_2 from group 2. Assume further that the mortality in group j can be described by the hazard functions $\alpha_j(t)$, $j = 1, 2$. We further assume that we have independent censoring. The goal is to estimate $A_j(t) = \int_0^t \alpha_j(s)\, ds$, $j = 1, 2$, and their difference $A_2(t) - A_1(t)$. Let $N_{j\cdot}(t) = \sum_i I(T_{ji} \leq t, \Delta_{ji} = 1)$, $j = 1, 2$, be the counting processes and $Y_{j\cdot}(t) = \sum_i I(t \leq T_{ji})$, $j = 1, 2$, the at risk processes. Put $n = n_1 + n_2$. We are going to let n_1 and n_2 tend to infinity from question (b) and onwards. We observe the processes in $t \in [0, \tau]$ with $\tau < \infty$.

(a) Give the two Nelson-Aalen estimators, $\hat{A}_j(t)$, corresponding to the two groups $j = 1, 2$. How would you estimate $A_2(t) - A_1(t)$?

(b) Show that

$$V_n(t) = n^{1/2}\{\hat{A}_2(t) - A_2(t) - (\hat{A}_1(t) - A_1(t)\}$$

can be written as

$$\tilde{M}(t) + R(t),$$

where $\tilde{M}(t)$ is a martingale and

$$R(t) = n^{1/2}\left\{\int_0^t \{J_2(s) - 1\}\alpha_2(s)\, ds - \int_0^t \{J_1(s) - 1\}\alpha_1(s)\, ds\right\},$$

where $J_j(t) = I(Y_{j\cdot}(t) > 0)$, $j = 1, 2$.

We assume that $R(t)$ converges uniformly in probability towards 0, for $t \in [0, \tau]$.

(c) Show that $V_n(t)$ converges in distribution to a Gaussian martingale, assuming that the needed Lindberg condition is fulfilled.

(d) Identify the asymptotical variance, and give an estimator of it.

(e) Use the results in (d) to construct a 95% confidence interval for $A_2(u) - A_1(u)$, where u is a fixed chosen time point.