Competing risks

Exercises

Exercise 1 : Independent latent event times

Consider two event times T_1 and T_2 with joint survival function

$$\begin{aligned} S(t_1, t_2) &= \mathrm{pr}(T_1 > t_1, T_2 > t_2\}) \\ &= \exp\left(1 - a_1 t_1 - a_2 t_2 - \exp(a_{12}(a_1 t_1 + a_2 t_2))\right) \end{aligned}$$

where $a_1, a_2 > 0$ and $a_{12} > -1$ measures the degree of dependence between T_1 and T_2. Assume a competing risks setting where we observe $T = T_1 \wedge T_2$ and the cause indicator $\varepsilon = 1 + I(T = T_2)$.

(a) Calculate the cause-specific hazard functions

$$\alpha_k(t) = \lim_{h \to 0} \frac{\mathrm{pr}(T_k < t + h | T_1 \geq t, T_2 \geq t)}{h}, \; k = 1, 2$$

(b) Write up the likelihood based on the observed data (T, ε) in terms of the cause-specific hazards.

(c) Now assume that $\tilde{T}_1$ and $\tilde{T}_2$ are independent with the cause-specific (and net) hazards $\alpha_k(t)$ from above, i.e.,

$$\lim_{h \to 0} \frac{\mathrm{pr}(\tilde{T}_k < t + h | \tilde{T}_1 \geq t, \tilde{T}_2 \geq t)}{h} = \lim_{h \to 0} \frac{\mathrm{pr}(\tilde{T}_k < t + h | \tilde{T}_k \geq t)}{h} = \alpha_k(t).$$

What does the joint survivor function, $\tilde{S}(t_1, t_2) = \mathrm{pr}(\tilde{T}_1 > t_1, \tilde{T}_2 > t_2)$, look like? Write up the likelihood for the observed data. $(\tilde{T} = \tilde{T}_1 \wedge \tilde{T}_2, \tilde{\varepsilon} = 1 + I(\tilde{T} = \tilde{T}_2))$

(d) Comparing the two models and likelihoods above, would you suggest using the estimated value of a_{12} to measure the degree of dependence between T_1 and T_2?

Exercise 2 (MS 10.1 + applied exercise) : "Cause-specific Kaplan-Meier"

Consider a competing risks situation where one observes the (continuous) event times T_i and the causes $\varepsilon_i \in \{1,2\}$ for $i = 1, \ldots, n$.

(a) Let $N_{\bullet,k}(t) = \sum_{i=1}^{n} I(T_i \leq t, \varepsilon_i = k)$ and $Y_\bullet = \sum_{i=1}^{n} I(T_i \geq t)$ and define

$$G_k(t) = \prod_{s \leq t} \left(1 - \frac{dN_{\bullet k}(s)}{Y_\bullet(s)}\right) = \prod_{j=1}^{N_{\bullet k}(t)} \left(1 - \frac{1}{Y_\bullet(\tau_j)}\right),$$

where $\tau_1, \ldots, \tau_{N_{\bullet k}(t)}$ are the observed type k event times in $[0,t]$ (no ties). $G_k(t)$ can be thought of as a cause-specific Kaplan-Meier estimator. Show, however, that it will not generally be a valid estimator of $1 - F_k(t)$ where $F_k(t) = pr(T \leq t, \varepsilon = k)$ is the cumulative incidence for cause k.

(b) The dataset `sir.adm` contains data on a random subsample of 747 intensive care unit patients from the SIR 3 (Spread of nonsocomial Infections and Resistant pathogens) cohort collected to examine the effect of hospital-acquired infections in intensive care (Wolkewitz et al., 2008). Competing endpoints are discharge from the unit and death on the unit.

Load the data with the command

```
sir.adm <- read.csv2("http://publicifsv.ku.dk/~frank/data/sir.adm.csv")
```

Data dictionary

Name	Content
time	length of stay (days)
status	0, censored before end of unit stay; 1, discharged (alive); 2 death on unit
pneu	pneumonia status on admission; 0 no pneumonia, 1 pneumonia

We will study the impact of pneumonia on on-unit mortality. Pneumonia is a severe infection, suspected to increase mortality. Death is the event of interest and discharge is the competing event.

(b1). Estimate the cause-specific cumulative hazards for both unit death and discharge by the Nelson-Aalen estimator. Plot the cumulative hazards for patients with and without pneumomia at admission.

Looking at the plots (ignore sampling variability and confidence intervals for now), consider.

- Does pneumonia have an impact on the mortality rate?
- What about discharge? Do patients with pneumonia at admission stay longer at the unit?
- Based on your answers to the two points above, would you expect to see more or fewer patients with pneumonia die on unit than patients without pneumonia?

(b2). How many percent were not still at the intensive care unit after 50 days? Draw the curve for the overall probability of leaving the unit (composite event death or discharge).

(b3). Draw the 1-Kaplan-Meier cuves for on-unit death censoring for discharge, i.e. $1 - G_2$. How many percent died on unit within 50 days according to this method? Discuss the interpretation of the estimate.

(b4). Redo the analysis from question b3, but for live discharge from unit, i.e., consider $1 - G_1$. What is the sum of the two curves $1 - G_1$ and $1 - G_2$ (at 50 days) compared to the overall probability of leaving the unit in question ($b2$)?

(b5). Estimate the cumulative incidence of death and discharge for patients with and without pneumonia by the Aalen-Johansen product limit estimator. Plot the cumulative incidence curves. Do they agree with your expectations from Question 1?

(b6). What is the sum of the two curves (at 50 days) compared to the overall probability of leaving the unit in question ($b2$) and question ($b4$)?

Exercise 3 : Proportional cause-specific and subdistribution hazards are incompatible

Show that, in general, proportional cause-specific hazards (e.g., Cox) and proportional subdistribution hazards (e.g., Fine and Gray) are incompatible. Hint: Find a function $c(t)$ such that $\alpha_1^{\#}(t) = c(t)\alpha_1(t)$, where $\alpha_j^{\#}$ and α_j are the subdistribution and cause-specific hazards, respectively.

Exercise 4 : Fine and Gray models for all risks

With the Fine and Gray model, the cause 1 risk can be described without modelling the other causes. In applications, proportional subdistribution models are sometimes used for each cause separately. In this exercise, we illustrate that this approach is conceptually problematic.

Consider two competing risks, 1 and 2 (one of them will happen if we wait long enough) and a binary covariate X. Assume that both risks follow Fine and Gray models,

$$\alpha_k^{\#}(t, X) = \alpha_{0k}^{\#}(t)e^{\beta_k^{\#} X}.$$

Assume that the cause 1 coefficient, $\beta_1^{\#}$, and both the cause 1 and 2 risks for $X = 0$, $F_1(t|X = 0)$, and thus baseline subdistribution hazards $\alpha_{0k}^{\#}(t)$, are known.

(a) What is the probability of a type 2 event? Express the probability in terms of the known parameters.

(b) Express $\beta_2^{\#}$ as a function of the known parameters.