Lec 5: Survival Analysis & Cox Model

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Oct. 3, 2023

Life table.

Example dataset of an insurance company, where:

- n_i : # of policy holders at age i
- d_i : # of deaths

Age	n	d
30	n_{30}	d_{30}
31	n_{31}	d_{31}
$\vdots$	$\vdots$	$\vdots$
89	n_{89}	d_{89}

$$\boxed{\text{Target: estimate the "survival function" } S_i = \mathbb{P}(X \geq i)}$$

Notations:

- X : a typical lifetime of a population (random variable)
- $S_i = \mathbb{P}(X \geq i)$: survival function
- h_i : hazard rate, defined as

$$h_i = \frac{\mathbb{P}(X = i)}{\mathbb{P}(X \geq i)} = \frac{S_i - S_{i+1}}{S_i}.$$

MLE.

Model: for $i \in \{30, \cdots, 89\}$, a sample of size n_i is drawn from a conditional population with $X \geq i$, where d_i of them die within one year.

Log-likelihood: $\ell(h_{30}, \cdots, h_{89}) = \sum_{i=30}^{89} \left(d_i \log h_i + (n_i - d_i) \log(1 - h_i) \right)$

MLE for h_i: $\frac{\partial \ell}{\partial h_i} = 0 \Rightarrow \frac{d_i}{\hat{h}_i} - \frac{n_i - d_i}{1 - \hat{h}_i} = 0 \Rightarrow \hat{h}_i = \frac{d_i}{n_i}.$

MLE for S_i: $\quad \hat{S}_i = \prod_{j=30}^{i-1} (1-\hat{h}_j)$.

Similarly, for $i<j$, one can estimate

$$\hat{\mathbb{P}}(X \geq j \mid X \geq i) = \prod_{k=i}^{j-1} (1-\hat{h}_k).$$

$\boxed{\text{One year's data suffices to learn the survival functions}}$

Censored data.

An example survival data after a clinical trial:

$\{ 64,\ 73+,\ 160,\ 160,\ 185+,\ 1101,\ 1412+,\ \cdots \}$

($a+$. still alive after a days)

$\Longrightarrow$ Transform into a lifetable:

days	n	d	ℓ
t_1	n_1	d_1	ℓ_1
t_2	n_2	d_2	ℓ_2
$\vdots$	$\vdots$	$\vdots$	$\vdots$
t_m	n_m	d_m	ℓ_m

Notations:

- d_i : # of observed deaths at day t_i after the trial
- ℓ_i : # of lost followups at day t_i after the trial
- n_i : # of individuals known to have survived at the beginning of day t_i

$$n_i = \sum_{j \geq i} (d_j + \ell_j)$$

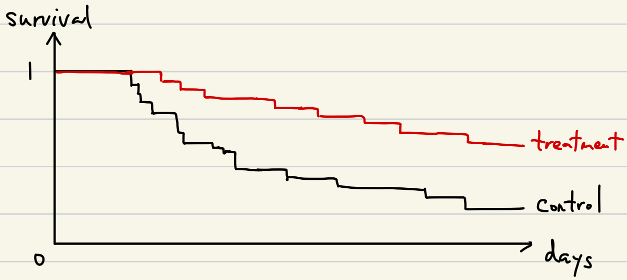
(for convenience, we assume that deaths & lost followups cannot happen simultaneously; i.e. for every i, either $d_i = 0$, or $\ell_i = 0$)

Target: estimate the survival function $S(t) = \mathbb{P}(X \geq t)$

Kaplan-Meier estimator.

$$\boxed{\begin{aligned}\hat{h}_i &= \hat{P}(X = t_i \mid X \geq t_i) = \frac{d_i}{n_i} \\ \hat{S}(t) &= \prod_{i: t_i < t} (1 - \hat{h}_i) = \prod_{i: t_i < t} \left(1 - \frac{d_i}{n_i}\right)\end{aligned}}$$

A Kaplan-Meier survival curve:



Derivation: empirical likelihood.

Let f be the pdf/pmf of X, and $S(t) = P(X \geq t)$

$$\text{log-likelihood}(S) = \sum_{i=1}^{m} \left(d_i \log(f(t_i)) + \ell_i \log(S(t_i)) \right)$$

likelihood of dying at t_i — likelihood of surviving until t_i

(An implicit assumption: probability of getting censored does not depend on the survival function)

Maximum value of $f(t_i)$ given S: $f(t_i) \leq S(t_i) - S(t_{i+1})$

$$\boxed{\text{Empirical likelihood: assume that } S \text{ has jumps only at } \{t_1, \cdots, t_n\}}$$

$$\text{empirical log-likelihood}(S) = \sum_{i=1}^{m} \left(d_i \log(S_i - S_{i+1}) + \ell_i \log S_i \right)$$

(Write $S_i := S(t_i)$)

Maximizing over $1 = S_1 \geq S_2 \geq \cdots \geq S_{m+1} \geq 0$

$\iff$ Maximizing over $h_1, \cdots, h_m \in [0,1]$, where

$$h_i = 1 - \frac{S_{i+1}}{S_i} \iff S_i = \prod_{j=1}^{i-1} (1-h_j).$$

Now empirical log-likelihood (h)

$$= \sum_{i=1}^{m} \left(d_i \log\left(h_i \prod_{j=1}^{i-1}(1-h_j)\right) + \ell_i \log \prod_{j=1}^{i-1}(1-h_j) \right)$$

$$= \sum_{i=1}^{m} \left(d_i \log h_i + \sum_{j=1}^{i-1} (d_i + \ell_i) \log(1-h_j) \right)$$

$$= \sum_{i=1}^{m} \left(d_i \log h_i + \sum_{k>i} (d_k + \ell_k) \log(1-h_i) \right)$$

(swapping the sum $\sum_i \sum_{j<i} = \sum_j \sum_{i>j}$)

$$= \sum_{i=1}^{m} \left(d_i \log h_i + (n_i - d_i - \ell_i) \log(1-h_i) \right)$$

(recall that $n_i = \sum_{k \geq i} (d_k + \ell_k)$)

F.O.C. for $h_i \implies \hat{h}_i = \dfrac{d_i}{n_i - \ell_i} = \dfrac{d_i}{n_i}$

(because either $d_i = 0$, or $\ell_i = 0$)

$$\implies \hat{S}_i = \prod_{j<i} (1 - \hat{h}_j) = \prod_{j<i} \left(1 - \frac{d_j}{n_j}\right)$$

$$\implies \hat{S}(t) = \max_{i:\, t_i < t} \hat{S}_{i+1} = \prod_{i:\, t_i < t} \left(1 - \frac{d_i}{n_i}\right).$$

Note: empirical likelihood is a special case of the nonparametric maximum likelihood (NPMLE).

Proportional hazards model (Cox model).

$\boxed{\text{Question: what if different individuals have different features?}}$

Data: a collection of $\{(t_i, \Delta_i, x_i)\}$ with hidden $\{(d_i, c_i)\}$:

- d_i : lifetime of individual i
- c_i : censored time of individual i
- $t_i = \min\{c_i, d_i\}$: death / censored time, whichever is earlier
  (right censoring)
- $\Delta_i = 1(d_i \le c_i)$. 1 if not censored, 0 if censored
  (true death)
- $x_i \in \mathbb{R}^p$: feature vector of individual i.

Continuous-time hazard rate

$$h(t) = \text{density of } (X = t \mid X \geq t) = \frac{f(t)}{S(t)}$$

$f(t)$ ← unconditional density of X

$$\Rightarrow \frac{d}{dt} \log S(t) = \frac{S'(t)}{S(t)} = -\frac{f(t)}{S(t)} = h(t)$$

$$\Rightarrow S(t) = \exp\left(-\int_0^t h(s)\, ds\right).$$

Proportional hazards model

$$h(t \mid x) = e^{\beta^T x} \underbrace{h(t)}_{\text{baseline hazard}}$$

log ratio: $\log \dfrac{h(t \mid x_1)}{h(t \mid x_2)} = \beta^T (x_1 - x_2)$

Target: estimate $\beta \in \mathbb{R}^p$.

Partial likelihood.

The Cox model is solved by maximizing the following partial likelihood;

$$L(\beta) = \prod_{i:\Delta_i=1} \left(\frac{e^{x_i^T\beta}}{\sum_{j\in R_i} e^{x_j^T\beta}} \right)$$

where :

- $\{i : \Delta_i = 1\}$ represents the occurrences of choose deaths
- R_i : the set of individuals at risk when i dies, i.e.

  $$R_i = \{j : t_j \geq t_i\}$$

- each term represents the probability of " i first dies among all individuals in the risk set R_i "
- no baseline hazard $h(t)$ in partial likelihood

Deriviation: profile likelihood

Complete likelihood

$$\underset{\substack{\uparrow \\ \text{target}}}{L(\beta}, \underset{\substack{\uparrow \\ \text{nuisance}}}{h)} \propto \prod_{i=1}^{n} \begin{cases} S(t_i|x_i)\,h(t_i|x_i), & \text{if } \Delta_i = 1 \\ S(t_i|x_i). & \text{if } \Delta_i = 0 \end{cases}$$

(Implicit assumption: c_i and d_i are independent conditioning on x_i)

$$= \prod_{i=1}^{n} \left[\exp(-e^{x_i^T\beta} H(t_i)) \left(e^{x_i^T\beta} h(t_i)\right)^{\Delta_i} \right]$$

$$\left(H(t) := \int_0^t h(s)\,ds \right)$$

Profile likelihood.

$$\boxed{pL(\beta) = \sup_h L(\beta, h)}$$

Computation of profile likelihood in Cox model:

1. Using empirical likelihood to assume that

h is supported on $\{t_1, \cdots, t_n\}$ & $H(t_i) = \sum_{j: t_j \le t_i} h(t_j)$

$$\Rightarrow L(\beta, h) = \prod_{i=1}^{n} \left[\exp\left(-e^{x_i^T \beta} \sum_{j: t_j \le t_i} h(t_j)\right) \left(e^{x_i^T \beta} h(t_i)\right)^{\Delta_i} \right]$$

2. F.O.C. for $h(t_i)$:

$$\frac{\partial(\log L)}{\partial h(t_i)} = \frac{\Delta_i}{h(t_i)} - \sum_{k: t_k \ge t_i} e^{x_k^T \beta} \begin{cases} = 0 & \text{if } h(t_i) > 0 \\ \le 0 & \text{if } h(t_i) = 0 \end{cases}$$

$$\Rightarrow h(t_i) = \begin{cases} 0 & \text{if } \Delta_i = 0 \\ \left(\sum_{k: t_k \ge t_i} e^{x_k^T \beta}\right)^{-1}, & \text{if } \Delta_i = 1 \end{cases}$$

3. A crucial identity: for above h,

$$\prod_{i=1}^{n} \exp\left(-e^{x_i^T \beta} \sum_{j: t_j \le t_i} h(t_j)\right)$$

$$= \exp\left(-\sum_{i=1}^{n} e^{x_i^T \beta} \sum_{j: t_j \le t_i} \frac{\Delta_j}{\sum_{k: t_k \ge t_i} e^{x_k^T \beta}}\right)$$

$$= \exp\left(-\sum_{j=1}^{n} \Delta_j \underbrace{\sum_{i: t_i \ge t_j} \frac{e^{x_i^T \beta}}{\sum_{k: t_k \ge t_i} e^{x_k^T \beta}}}_{=1}\right)$$

$$= \prod_{j=1}^{n} \left(\frac{1}{e}\right)^{\Delta_j}$$

4. Plug back to $L(\beta, h)$:

$$
\begin{aligned}
pL(\beta) &= \sup_h L(\beta, h) \\
&= \prod_{i=1}^{n} \left(\frac{1}{e} \frac{e^{x_i^T \beta}}{\sum_{k: t_k \geq t_i} e^{x_k^T \beta}} \right)^{\Delta_i} \\
&\propto \prod_{i: \Delta_i = 1} \left(\frac{e^{x_i^T \beta}}{\sum_{k \in R_i} e^{x_k^T \beta}} \right),
\end{aligned}
$$

agreeing with the partial likelihood.