

Survival analysis notes

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Chapter 1

Notation

Notation	Description
C_i	Random variable representing the time to censoring
$T_i = \min(X_i, C_i)$	Observable event time
$\delta_i = \mathbb{1}(T_i = X_i)$	Indicator variable equal to one if event time is a failure time
$P_\theta(X \leq t)$	Distribution function of X indexed by parameters θ
$S_X(t; \theta)$	Survival function for random variable X evaluated at t , parameters θ
$f_X(t; \theta)$	Density function for random variable X evaluated at t , parameters θ
$\lambda_X(t; \theta)$	Hazard function for random variable X evaluated at t , parameters θ

Table 1.1: List of notation used throughout the notes

Chapter 2

Introduction

This introduction is based in part on Klein, Moeschberger, et al. 2003, and in part on Aalen et al. 2008 plus Fleming and Harrington 2005.

Survival analysis is the modeling and analysis of time-to-event data; this means we will be studying how to model **nonnegative** random variables (time will always be measured in such a way so that the observations are nonnegative). Think about a clinical trial for a new COVID vaccine and how you might model the length of time between study entry and infection in each arm of the trial. Let X_i be the time from trial entry to infection for the i -th participant. These sorts of trials are typically run until a prespecified number of people have become infected. Let n be the total number of participants in the trial and let r be the prespecified number of infections. Let T_i be the observed infection time for the i -th participant. This means that for r participants, $T_i = X_i$, but for $n - r$ participants we know only that the time-to-infection is larger than the observed time. Let C_i denote the time from study entry for participant i to study end. Then $T_i = \min(X_i, C_i)$, and let $\delta_i = \mathbb{1}(T_i = X_i)$. The density of T_i is related to the joint probability for X_i and C_i , which is indexed by a possibly infinite dimensional parameter θ : $P_\theta(X_i > t, C_i > c)$. When $\delta_i = 1$, and $T_i = X_i$, the likelihood of the observation is

$$\left(-\frac{\partial}{\partial u} P_\theta(X_i > u, C_i > t) \right) \Big|_{u=t},$$

while the likelihood for $\delta_i = 0$ is

$$\left(-\frac{\partial}{\partial u} P_\theta(X_i > t, C_i > u) \right) \Big|_{u=t},$$

Then $T_i = C_i$ for the other $n - r$ participants. Under the null hypothesis that the vaccine has no effect, the population distribution function for all n participants for X_i, C_i is $P_\theta(X_1 > x, C_1 > c)$ (i.e. the distribution for survival times in the treatment group and the placebo

group is the same). Then the joint density for the observed infection times is as follows:

$$f_{T_1, \dots, T_n}(t_1, \dots, t_n; \theta) = n! \prod_{i=1}^r \left(-\frac{\partial}{\partial u} P_\theta(X_1 > u, C_1 > t_{(i)}) \right) \Big|_{u=t_{(i)}} \prod_{i=r+1}^n \left(\left(-\frac{\partial}{\partial u} P_\theta(X_1 > t_{(i)}, C_1 > u) \right) \Big|_{u=t_{(i)}} \right),$$

where $t_{(i)}$ is the i -th order statistic of the set $\{t_1, \dots, t_n\}$. Note that this is different from most other data analysis where missing observations are not expected to occur with much frequency. On the contrary, in survival analysis, missingness, both *truncation* and *censoring* are expected to occur with nearly every dataset, so much of our time will be spent ensuring our methods work when data arise with these peculiarities.

2.1 Independent censoring

Now suppose that $X_1 \perp C_1$, and that θ partitions into η and ϕ , such that

$$P_\theta(X_1 > x, C_1 > c) = P_\eta(X_1 > x) P_\phi(C_1 > c).$$

Then we can rewrite the joint observational density for T_i as:

$$\begin{aligned} f_{T_1, \dots, T_n}(t_1, \dots, t_n; \theta) &= n! \left(\prod_{i=1}^r f_{X_1}(t_{(i)}; \eta) \right) \prod_{i=r+1}^n P_\eta(X_1 > t_{(i)}) \\ &\quad \times \left(\prod_{i=1}^r P_\phi(C_1 > t_{(i)}) \right) \prod_{i=r+1}^n f_C(t_{(i)}; \phi). \end{aligned}$$

If we are only interested about inference about η , the parameters that govern the distribution of the true time-to-infection random variables, we can ignore the the distribution for the censoring random variables C_1 , and maximize the likelihood because, in η :

$$f_{T_1, \dots, T_n}(t_1, \dots, t_n; \eta) \propto \left(\prod_{i=1}^r f_{X_1}(t_{(i)}; \eta) \right) \prod_{i=r+1}^n P_\eta(X_1 > t_{(i)})$$

We will talk in more detail about censoring in the coming lectures.

2.2 Mean time to failure

Aalen et al. 2008 notes that we cannot even compute a simple mean in this situation, so something like a t-test will be useless. As an aside, let's try to compute a mean from the data above. Let $\bar{T} = \frac{1}{n} \sum_{i=1}^n T_i$. We can show that $\lim_{n \rightarrow \infty} \bar{T} \leq \mathbb{E}[X_i]$ with probability 1.

Proof. Let $T_i = X_i \mathbb{1}(X_i \leq C_i) + C_i \mathbb{1}(X_i > C_i)$. Then by the SLLN $\bar{T} \xrightarrow{\text{a.s.}} \mathbb{E}[T_i]$.

$$\begin{aligned} \mathbb{E}[T_i] &= \mathbb{E}[X_i \mathbb{1}(X_i \leq C_i)] + \mathbb{E}[C_i \mathbb{1}(X_i > C_i)] \\ &\leq \mathbb{E}[X_i \mathbb{1}(X_i \leq C_i)] + \mathbb{E}[X_i \mathbb{1}(X_i > C_i)] = \mathbb{E}[X_i] \end{aligned}$$

□

2.3 Survival function

How can we compute the mean time to infection then? One way to estimate the mean time to infection is to first estimate the function $S_{X_i}(t; \theta) = P_\theta(X_i > t)$, which is also known as the *survival function*. Recall this fact about non-negative random variables $X_i \geq 0$ w.p. 1:

$$\mathbb{E}[X_i] = \int_0^\infty P_\theta(X_i > t) dt$$

This follows from an application of Fubini's theorem applied to the integral:

$$\begin{aligned} \mathbb{E}[X_i] &= \int_0^\infty u dP_{X_i}(u; \theta) \\ &= \int_0^\infty \int_0^\infty \mathbb{1}(0 \leq t \leq u) dt dP_{X_i}(u; \theta) \\ &= \int_0^\infty \int_0^\infty \mathbb{1}(0 \leq t \leq u) dP_{X_i}(u; \theta) dt \\ &= \int_0^\infty P_\theta(X_i > t) dt \end{aligned}$$

2.3.1 Properties of the survival function

Let $F_{X_i}(t; \theta) = P_\theta(X_i \leq t)$. Then because the survival function is defined as $S_{X_i}(t; \theta) = 1 - F_{X_i}(t; \theta)$ (also known as the complementary CDF) the survival function inherits its properties from the CDF. The survival function:

1. $S_{X_i}(t; \theta)$ is a nonincreasing function
2. $S_{X_i}(0; \theta) = 1$
3. $\lim_{t \rightarrow \infty} S_{X_i}(t; \theta) = 0$
4. Has lefthand limits:

$$\lim_{s \nearrow t} S_{X_i}(s; \theta) = S_{X_i}(t-; \theta).$$

5. Is right continuous:

$$\lim_{s \searrow t} S_{X_i}(s; \theta) = S_{X_i}(t; \theta).$$

An example of a discrete survival function is shown in Figure 2.1.

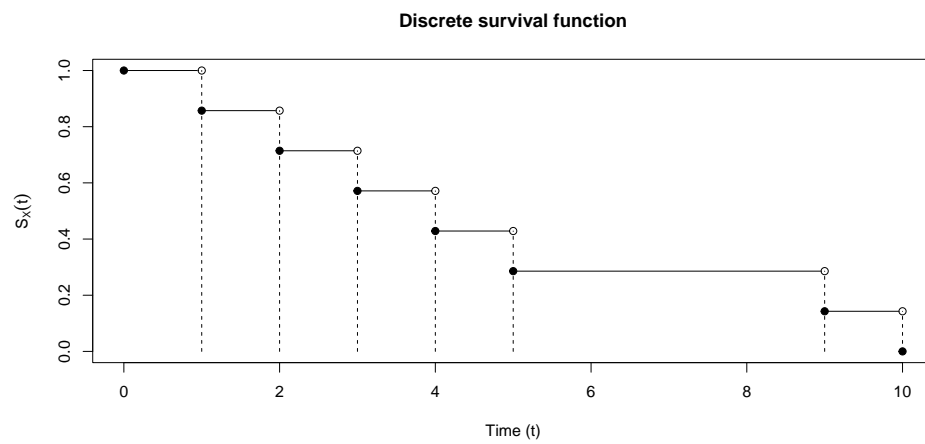


Figure 2.1: Example plot of a survival function for a discrete survival time, bounded between $[0, 10]$

2.4 Hazard function

Another way to characterize the random variable X_i is the *hazard function*, which is typically denoted as $\lambda(t)$ or $h(t)$ and is defined as

$$\begin{aligned}\lambda_{X_i}(t) &= \lim_{\Delta t \searrow 0} \frac{1}{\Delta t} \mathbb{P}_\theta(t \leq X_i < t + \Delta t \mid X_i \geq t) \\ &= \lim_{\Delta t \searrow 0} \frac{1}{\Delta t} \frac{\mathbb{P}_\theta(t \leq X_i < t + \Delta t)}{\mathbb{P}_\theta(X_i \geq t)}\end{aligned}$$

First, note that we can define $\mathbb{P}_\theta(X_i \geq t)$ in terms of the survival function as:

$$\mathbb{P}_\theta(X_i \geq t) = \lim_{s \nearrow t} S_{X_i}(s; \theta).$$

Using the notation introduced in Section 2.3.1, we can write this as

$$\mathbb{P}_\theta(X_i \geq t) = S_{X_i}(t-; \theta).$$

Of course, when X_i is absolutely continuous, $S_{X_i}(t-; \theta) = S_{X_i}(t; \theta)$, but when X_i is discrete, or mixed discrete and continuous, as noted above, it is not true in general that the survival function is left-continuous.

A few things to note about $\lambda_{X_i}(t; \theta)$: when X_i is an absolutely continuous random variable, which occurs when we're considering survival in continuous time, we can write this in terms of the probability density function $f_{X_i}(t; \theta)$ and the cumulative distribution function $F_{X_i}(t; \theta)$:

$$\begin{aligned}\lambda_{X_i}(t) &= \lim_{\Delta t \searrow 0} \frac{1}{\Delta t} \frac{\mathbb{P}_\theta(t \leq X_i < t + \Delta t)}{\mathbb{P}_\theta(X_i \geq t)} \\ &= \lim_{\Delta t \searrow 0} \frac{F_{X_i}(t + \Delta t; \theta) - F_{X_i}(t; \theta)}{\Delta t} \times \frac{1}{1 - F_{X_i}(t; \theta)} \\ &= \frac{f_{X_i}(t; \theta)}{1 - F_{X_i}(t; \theta)}.\end{aligned}$$

Let's examine how the survival function and the hazard function fit together.

$$\lambda_{X_i}(t) = \frac{f_{X_i}(t; \theta)}{S_{X_i}(t-; \theta)}.$$

Note that we can write the hazard function in terms of the survival function instead of the density, when X_i is absolutely continuous:

$$\begin{aligned}\lambda_{X_i}(t) &= \lim_{\Delta t \searrow 0} \frac{1}{\Delta t} \frac{\mathbb{P}_\theta(t \leq X_i < t + \Delta t)}{\mathbb{P}_\theta(X_i \geq t)} \\ &= \lim_{\Delta t \searrow 0} \frac{S_{X_i}(t; \theta) - S_{X_i}(t + \Delta t; \theta)}{\Delta t} \times \frac{1}{S_{X_i}(t; \theta)} \\ &= -\frac{d}{dt} S_{X_i}(t; \theta) / S_{X_i}(t; \theta).\end{aligned}$$

This implies that

$$\lambda_{X_i}(t) = -\frac{d}{dt} \log S_{X_i}(t; \theta).$$

If we integrate both sides, we get another important identity in survival analysis:

$$\int_0^u \frac{d}{dt} \log S_{X_i}(t; \theta) dt = - \int_0^u \lambda_{X_i}(t) dt \quad (2.1)$$

$$\log S_{X_i}(u; \theta) - \log S_{X_i}(0; \theta) = - \int_0^u \lambda_{X_i}(t) dt \quad \text{note } S_{X_i}(0; \theta) = 1 \quad (2.2)$$

$$S_{X_i}(u; \theta) = \exp\left(- \int_0^u \lambda_{X_i}(t) dt\right) \quad (2.3)$$

2.4.1 Properties of the hazard function

The relationship $S_{X_i}(u; \theta) = \exp\left(- \int_0^u \lambda_{X_i}(t) dt\right)$ and the properties of the survival function reveal the following facts about the hazard function and highlight its differences with a probability density.

1. $\lim_{t \rightarrow \infty} S_{X_i}(t; \theta) = 0$ implies that $\lim_{t \rightarrow \infty} \int_0^t \lambda_X(u) du = \infty$
2. Given that $S_{X_i}(t; \theta)$ is a nonincreasing function, $\lambda_X(t) \geq 0$ for all t .

So unlike a probability density function, $\lambda_X(t)$ isn't integrable over the support of the random variable.

2.5 Density function for survival time

Given that we have $S_{X_i}(t; \theta)$ and $\lambda(t) = \frac{f_{X_i}(t; \theta)}{S_{X_i}(t-; \theta)}$, we can recover the density, $f_{X_i}(t; \theta)$ easily:

$$f_{X_i}(t; \theta) = \lambda_{X_i}(t) S_{X_i}(t-; \theta)$$

2.6 Cumulative hazard function

One final important quantity that describes a survival distribution is that of *cumulative hazard*, which we'll denote as $\Lambda_{X_i}(t)$, though it is also denoted as $H(t)$ in Klein, Moeschberger, et al. 2003. This is defined as you might expect:

$$\Lambda_{X_i}(t) = \int_0^t \lambda_{X_i}(u) du.$$

It has the important property that for any absolutely continuous failure time X_i with a given cumulative hazard function, the random variable $Y_i = \Lambda_{X_i}(X_i)$ is exponentially distributed

with rate 1. The derivation is straightforward. Remember that $P(X_i > t) = \exp(-\Lambda_{X_i}(t))$

$$\begin{aligned} P(\Lambda_{X_i}(X_i) > t) &= P(X_i > \Lambda_{X_i}^{-1}(t)) \\ &= \exp(-\Lambda_{X_i}(\Lambda_{X_i}^{-1}(t))) \\ &= \exp(-t) \end{aligned}$$

2.7 Discrete survival time

We've been working with continuous survival times until now. If X_i is a discrete random variable with support on $\{t_1, t_2, \dots\}$, we lose some of the tidyness of the previous derivations. We can define the distribution of X_i in terms of the survival function, $P_\theta(X_i > t)$. First let $p_j = P_\theta(X_i = t_j)$, so

$$S_{X_i}(t; \theta) = P_\theta(X_i > t) = \sum_{j|t_j > t} p_j$$

We can also define the hazard function for a discrete random variable:

$$\lambda_{X_i}(t_j) = \frac{p_j}{S_{X_i}(t_{j-1}; \theta)} = \frac{p_j}{p_j + p_{j+1} + \dots}$$

Note that $p_j = S_{X_i}(t_{j-1}; \theta) - S_{X_i}(t_j; \theta)$, then

$$\lambda_{X_i}(t_j) = 1 - \frac{S_{X_i}(t_j; \theta)}{S_{X_i}(t_{j-1}; \theta)}.$$

If we let $t_0 = 0$ then $S_{X_i}(t_0; \theta) = 1$. This allows us to write the survival function in a sort of telescoping product:

$$\begin{aligned} P_\theta(X_i > t_j) &= P_\theta(X_i > t_0) \frac{P_\theta(X_i > t_1)}{P_\theta(X_i > t_0)} \frac{P_\theta(X_i > t_2)}{P_\theta(X_i > t_1)} \cdots \frac{P_\theta(X_i > t_j)}{P_\theta(X_i > t_{j-1})} \\ &= 1 \frac{S_{X_i}(t_1; \theta)}{S_{X_i}(t_0; \theta)} \frac{S_{X_i}(t_2; \theta)}{S_{X_i}(t_1; \theta)} \cdots \frac{S_{X_i}(t_j; \theta)}{S_{X_i}(t_{j-1}; \theta)} \end{aligned}$$

This yields another way to write $S_{X_i}(t; \theta)$:

$$S_{X_i}(t; \theta) = \prod_{j|t_j \leq t} (1 - \lambda_{X_i}(t_j)). \quad (2.4)$$

It turns out that we can write the survival function for continuous random variables in the same way.

2.7.1 Connection between discrete and continuous survival functions

Recall the definition of the hazard function:

$$\lambda_{X_i}(t) = \lim_{\Delta t \searrow 0} \frac{1}{\Delta t} \mathbb{P}_\theta(t \leq X < t + \Delta t \mid X \geq t)$$

Note that $\lambda_{X_i}(t) \Delta t$ is approximately $\mathbb{P}_\theta(t \leq X < t + \Delta t \mid X \geq t)$. Let \mathcal{T} be a partition of $(0, \infty)$ with partition size Δt , $t_0 = 0$:

$$\mathcal{T} = \bigcup_{j=0}^{\infty} [t_j, t_j + \Delta t).$$

Then we can use Equation (2.4) to represent the survival function:

$$S_{X_i}(t; \theta) = \prod_{j \mid t_j + \Delta t \leq t} (1 - \lambda_{X_i}(t_j) \Delta t). \quad (2.5)$$

We can show that as the partition of the time domain gets finer and finer, we will recover $S_{X_i}(t; \theta) = \exp(-\int_0^t \lambda_{X_i}(u) du)$

$$S_{X_i}(t; \theta) = \prod_{j \in \mathcal{T} \mid t_j + \Delta t \leq t} (1 - \lambda_{X_i}(t_j) \Delta t) \quad (2.6)$$

$$\log S_{X_i}(t; \theta) = \sum_{j \in \mathcal{T} \mid t_j + \Delta t \leq t} \log(1 - \lambda_{X_i}(t_j) \Delta t) \quad (2.7)$$

We use the Taylor expansion of $\log(1 - \lambda_{X_i}(t_j) \Delta t)$ for small $\lambda_{X_i}(t_j) \Delta t$, assuming that $\lambda_{X_i}(t)$ is sufficiently well-behaved for all t .

$$\log(1 - \lambda_{X_i}(t_j) \Delta t) \approx -\lambda_{X_i}(t_j) \Delta t.$$

Then

$$\log S_{X_i}(t; \theta) \approx \sum_{j \in \mathcal{T} \mid t_j + \Delta t \leq t} -\lambda_{X_i}(t_j) \Delta t \quad (2.8)$$

As

$$\lim_{\Delta t \searrow 0} \sum_{j \in \mathcal{T} \mid t_j + \Delta t \leq t} -\lambda_{X_i}(t_j) \Delta t = -\int_0^t \lambda_{X_i}(u) du.$$

So, $S_{X_i}(t; \theta) = \exp(-\int_0^t \lambda_{X_i}(u) du)$, or

$$S_{X_i}(t; \theta) = \exp(-\lambda_{X_i}(t)) \quad (2.9)$$

2.8 Mean residual lifetime

We also might be interested in the *mean residual lifetime* (mrl for short), or the expected lifetime given survival up to a certain point:

$$\mathbb{E}[X_i - x \mid X_i > x].$$

We can compute this for an absolutely continuous random variable by using the survival function:

$$\frac{\int_x^\infty (u - x) f_{X_i}(u; \eta) du}{S_{X_i}(x; \eta)} = \frac{\int_x^\infty S_{X_i}(u; \eta) du}{S_{X_i}(x; \eta)}$$

To derive the mrl in terms of the survival function, note that we can use Fubini again on the numerator (Exercise 1), or we can use integration by parts:

$$\begin{aligned} \int_x^\infty (u - x) f_{X_i}(u) du &= - \int_x^\infty (u - x) \frac{d}{du} S_{X_i}(u) du \\ &= -(u - x) S_{X_i}(u) \Big|_{u=x}^\infty + \int_x^\infty S_{X_i}(u) du \end{aligned}$$

and use the fact that $\lim_{u \rightarrow \infty} S_{X_i}(u) = 0$. We also need the following:

$$\lim_{u \rightarrow \infty} u P(X_i > u) = 0. \quad (2.10)$$

This is a pretty weak condition, random variables with second moments satisfy this condition (Exercise 2), as do random variables with only first moments. It turns out that under this condition we'll have a weak law of large numbers (see §7.1 in Resnick 2019).

Suppose we assume that $\mathbb{E}[X] \leq \infty$. Then we can write:

$$\mathbb{E}[X] = \mathbb{E}[X \mathbb{1}(X \leq n)] + \mathbb{E}[X \mathbb{1}(X > n)]$$

Note that if we define $X_n = X \mathbb{1}(X \leq n)$ then

$$X_1(\omega) \leq X_2(\omega) \leq \dots \leq X_k(\omega) \leq \dots$$

By the Monotone Convergence Theorem (MCT), $\mathbb{E}[X_n] \rightarrow \mathbb{E}[X]$. Then

$$\begin{aligned} \mathbb{E}[X] &= \mathbb{E}[X_n] + \mathbb{E}[X \mathbb{1}(X > n)] \\ &\geq \mathbb{E}[X_n] + \mathbb{E}[n \mathbb{1}(X > n)] \\ &= \mathbb{E}[X_n] + nP(X > n) \end{aligned}$$

This leads to the system of inequalities:

$$\mathbb{E}[X] - \mathbb{E}[X_n] \geq nP(X > n) \geq 0.$$

By the MCT $\mathbb{E}[X] - \mathbb{E}[X_n] \rightarrow 0$ so

$$\lim_{n \rightarrow \infty} nP(X_i > n) = 0.$$

However, there are random variables for which $\mathbb{E}[X_i]$ does not exist, but do satisfy Equation (2.10) (see the end of §7.1 in Resnick 2019).

2.9 Examples

The first example we'll run through is for an exponentially distributed survival time:

$$X_i \stackrel{\text{iid}}{\sim} \text{Exp}(\lambda).$$

The survival function is $S_X(t) = e^{-\lambda t}$. We can read off from this that $\Lambda(t) = \lambda t$. What's the hazard function? Let's plot the hazard function. What does this imply about the exponential distribution (memorylessness)? The mean lifetime is $\frac{1}{\lambda}$. The mean residual lifetime is:

$$\begin{aligned} \frac{\int_t^\infty e^{-\lambda u} du}{e^{-\lambda t}} &= \frac{1}{\lambda} \frac{e^{-\lambda t} du}{e^{-\lambda t}} \\ &= \frac{1}{\lambda}. \end{aligned}$$

This is a consequence of the memoryless property of the exponential distribution.

Another parametric distribution for survival times is the Weibull.

$$X_i \stackrel{\text{iid}}{\sim} \text{Weibull}(\gamma, \alpha).$$

The survival function:

$$S_X(t) = \exp(-\gamma t^\alpha).$$

Again, we have that $\Lambda(t) = \gamma t^\alpha$, so we can take the derivative with respect to t to get the hazard:

$$\lambda(t) = \gamma \alpha t^{\alpha-1}.$$

This is more flexible than the exponential distribution, though note that for $\alpha = 1$, $X_i \sim \text{Exponential}(\gamma)$, so the Weibull family contains the exponential family as a special case. The α parameter allows for the hazard rate to have more flexibility than the exponential. If $\alpha > 1$, the hazard rate is increasing in t . This corresponds to an aging process, whereby the longer something has survived, the higher the rate of failure. If $\alpha < 1$, the hazard rate is decreasing in t . This might correspond to something like the hazard for SIDS, which is quite high for

children before 1 year old, but drops off rapidly after 1. Let's compute the mean lifetime, $\mathbb{E}[X] = \int_0^\infty S_X(t)dt$, using a v -sub, $v = t^\alpha$, so $v^{\frac{1}{\alpha}} = t \rightarrow \frac{1}{\alpha}v^{\frac{1}{\alpha}-1}dv = dt$:

$$\begin{aligned}\int_0^\infty \exp(-\gamma t^\alpha)dt &= \frac{1}{\alpha} \int_0^\infty v^{\frac{1}{\alpha}-1} \exp(-\gamma v)dv \\ &= \frac{1}{\alpha} \frac{1}{\gamma^{\frac{1}{\alpha}}} \Gamma\left(\frac{1}{\alpha}\right) \\ &= \frac{\Gamma\left(\frac{1}{\alpha} + 1\right)}{\gamma^{\frac{1}{\alpha}}}\end{aligned}$$

The mean residual lifetime is a bit more involved. Let $v = \gamma u^\alpha$ so $\left(\frac{v}{\gamma}\right)^{1/\alpha} = u \rightarrow \gamma^{-1/\alpha} \frac{1}{\alpha} v^{\frac{1}{\alpha}-1} dv = du$:

$$\begin{aligned}\int_t^\infty \exp(-\gamma u^\alpha)du &= \gamma^{-1/\alpha} \frac{1}{\alpha} \int_{\gamma t^\alpha}^\infty v^{\frac{1}{\alpha}-1} \exp(-v)dv \\ &= \gamma^{-1/\alpha} \frac{1}{\alpha} \Gamma\left(\frac{1}{\alpha}, \gamma t^\alpha\right),\end{aligned}$$

where $\Gamma\left(\frac{1}{\alpha}, \gamma t^\alpha\right)$ is the upper incomplete Gamma function.

Chapter 3

Censoring and truncation

Now let's delve into more detail about censoring, and how the likelihood can be built up from the hazard function and the survival function. Klein, Moeschberger, et al. 2003 define censoring as imprecise knowledge about an event time. If we observe a failure or an event exactly, the observation is not censored, but if we know only that an observation occurred within a range of values, we say the observation is censored. Let X_i , as usual, be our failure time, which is not completely observed. Instead if:

- $X_i \in [U, \infty)$, the observation is *right censored*
- $X_i \in [0, V)$, the observation is *left censored*
- $X_i \in [U, V)$, the observation is *interval censored*

3.1 Right censoring

Right censoring occurs when a survival time is known to be larger than a given value. This is the most common censoring scenario in survival analysis.

Recall our definition in Chapter 2:

- Let X_i be the time to failure, or time to event for individual i .
- Let C_i be the time to censoring. It may be helpful to think about C_i as the time to investigator measurement.
- Let $\delta_i = \mathbb{1}(X_i \leq C_i)$.
- Let $T_i = \min(X_i, C_i)$.

Given our definitions in Section 3.1, when an observation is censored, or when a measurement is taken of the survival time before the event has happened, $\delta_i = 0$ and $T_i = C_i$.

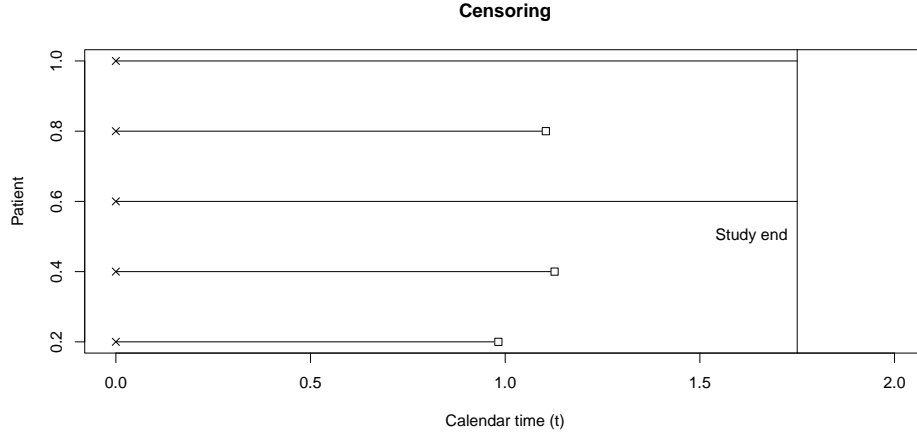


Figure 3.1: Example of Type I censoring.

3.1.1 Type I censoring

The simplest censoring scenario is one in which all individuals have the same, nonrandom censoring time. Imagine a study is designed to follow 5 startups that are spun out of a tech incubator to study how long it takes a company to land its first contract. This information will be used for designing investments 2 years from the study date, so the study has a length of 1.75 years. We can say that all observations will have to have occurred, or not, by 1.75 years.

Figure 3.1 shows a potential result of the study, where 2 out of the 5 companies have not landed a contract. In this case,

- For all individuals such that $\delta_i = 0 \implies X_i > C$
- $\delta_i = 1 \implies T_i = X_i$.

3.1.2 Generalized type I censoring

A more general scenario, which is closer to most examples in clinical trials, is when each individual has a different study entry time and the investigator has a preset study end time. This is called generalized Type I censoring. These study entry times are typically assumed to be independent of the survival time. This is shown in Figure 3.2. When study entry is independent from survival time, the analysis proceeds as shown in Figure 3.3. For generalized type I censoring,

- For all individuals such that $\delta_i = 0 \implies X_i > C_i$

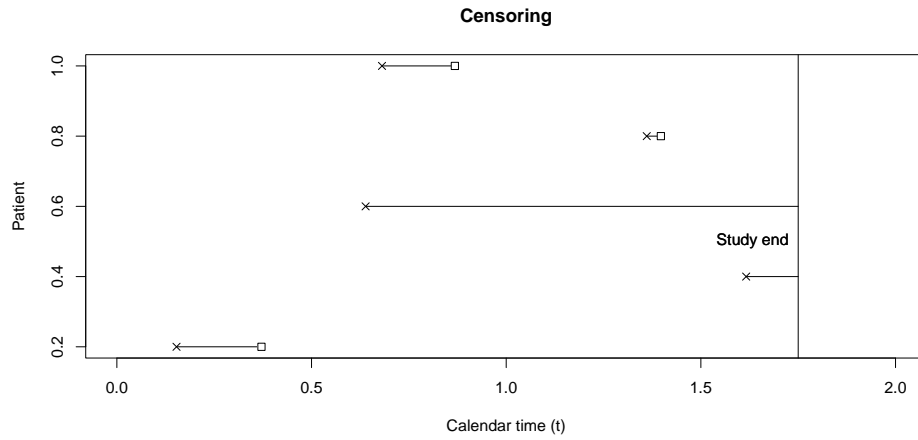


Figure 3.2: Example of generalized Type I censoring, where each individual has a separate study entry time.

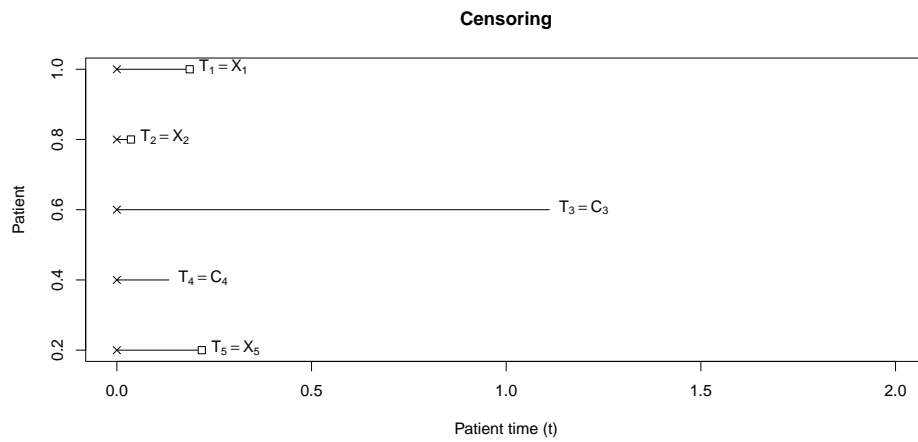


Figure 3.3: Example of generalized Type I censoring, viewed in patient time.

- $\delta_i = 1 \implies T_i = X_i$.

This is different from Type I censoring in that each individual has a different censoring time.

3.1.3 Type II censoring

Type II censoring occurs when all units have the same study entry time, but researchers design the study to end when $r < n$ units fail out of n total units under observation.

- For the first r , lucky or unlucky participants, $\delta_i = 1 \implies T_i = X_{(i)}$ or the i^{th} order statistic.
- For the remaining $n - r$ individuals, $\delta_i = 0 \implies X_i > X_{(r)}$.

3.1.4 Generalized Type II censoring

You may be wondering, what happens when units have differing start times but we want to end the trial after the r -th failure? It turns out that this was not a solved problem until Rühl et al. 2023, which was quite surprising to me.

3.1.5 Independent censoring

A third type of censoring, helpfully called independent censoring, takes $X_i \perp\!\!\!\perp C_i$, and thus conclusions similar to those of generalized type I censoring can be drawn:

- For all individuals such that $\delta_i = 0 \implies X_i > C_i$
- $\delta_i = 1 \implies T_i = X_i$.

3.2 Noninformative censoring

All of the previous censoring scenarios can be summarized as noninformative censoring. Let the parameters indexing the censoring distribution be ϕ , while the parameters indexing the failure time distribution are η . Noninformative censoring is defined as the following equality:

$$\lambda_{X_i}(t) = \lim_{\Delta t \searrow 0} \frac{1}{\Delta t} \mathbb{P}_{\eta, \phi}(t \leq X_i < t + \Delta t \mid X_i \geq t, C_i \geq t) \quad (3.1)$$

Note that this implies the following:

$$\mathbb{P}_{\eta}(t \leq X_i < t + \Delta t \mid X_i \geq t) = \mathbb{P}_{\eta, \phi}(t \leq X_i < t + \Delta t \mid X_i \geq t, C_i \geq t). \quad (3.2)$$

which is equivalent to writing that failure

For independent censoring, Equation (3.2) holds, given that $P_{\eta,\phi}(X_i > t, C_i > c) = P_\eta(X_i > t)P_\phi(C_i > c)$ and that η and ϕ are *variationally independent*.

This means that the parameter space $\Omega_{\eta,\phi}$ is the Cartesian product of the parameter space for η and ϕ .

Definition 3.2.1. Variational independence Let $\eta \in \Omega_\eta$ and $\phi \in \Omega_\phi$. The joint space is denoted as $\Omega_{\eta,\phi}$. If $\Omega_{\eta,\phi} = \Omega_\eta \times \Omega_\phi$, η and ϕ are variationally independent. In other words, the range for η does not change given a value for ϕ .

Under independent censoring, the observable hazard for uncensored failure times is as follows:

$$\frac{-\frac{\partial}{\partial u}P_{\eta,\phi}(X_i > u, C_i > t-) |_{u=t}}{P_{\eta,\phi}(X_i > t-, C_i > t-)} = \frac{-\frac{d}{du}S_{X_i}(u; \eta)}{S_{X_i}(t-; \eta)} \quad (3.3)$$

Here's an example that demonstrates the nonidentifiability of the joint distribution for censoring and failure time:

Example 3.2.1. Dependent failure and censoring

Let $P_{\theta,\alpha,\mu}(X_i > x, C_i > c) = \exp(-\alpha x - \mu c - \theta xc)$. We can find the marginal survival functions just by evaluating $P_{\theta,\alpha,\mu}(X_i > x, C_i > 0)$ and vice-versa, which yields:

$$\begin{aligned} P_\alpha(X_i > x) &= \exp(-\alpha x) \\ P_\mu(C_i > c) &= \exp(-\mu c) \end{aligned}$$

Both of these distributions have constant hazards. However, the observable hazard is the following:

$$\begin{aligned} \frac{-\frac{\partial}{\partial u}P_{\theta,\alpha,\mu}(X_i > u, C_i > t-) |_{u=t}}{P_{\theta,\alpha,\mu}(X_i > t-, C_i > t-)} &= \alpha + \theta t \\ \frac{-\frac{\partial}{\partial u}P_{\theta,\alpha,\mu}(X_i > t-, C_i > u) |_{u=t}}{P_{\theta,\alpha,\mu}(X_i > t-, C_i > t-)} &= \mu + \theta t \end{aligned}$$

This leads to an observable survival function:

$$\begin{aligned} S_{X_i}(x; \alpha, \theta) &= \exp(-\alpha x - \theta x^2/2) \\ S_{C_i}(c; \mu, \theta) &= \exp(-\mu c - \theta c^2/2) \end{aligned}$$

If we mistakenly assume that the failure time and the censoring time are independent we'll get the following joint distribution:

$$S_{X_i}(x; \alpha, \theta)S_{C_i}(c; \mu, \theta) \neq \exp(-\alpha x - \mu c - \theta xc).$$

However, if we calculate the true observable survival function $P_{\theta,\alpha,\mu}(X_i > x, C_i > X_i -)$ we get:

$$\int_x^\infty -\frac{\partial}{\partial u} P_{\theta,\alpha,\mu}(X_i > u, C_i > t-) \big|_{u=t} dt = \int_x^\infty (\alpha + \theta t) \exp(-\alpha t - \mu t - \theta t^2) dt$$

while the observable survival function implied by the erroneously assumed independent distributions is:

$$\begin{aligned} \int_x^\infty -\frac{\partial}{\partial u} S_{X_i}(u; \alpha, \theta) S_{C_i}(t-; \mu, \theta) \big|_{u=t} dt &= \int_x^\infty \left(-\frac{d}{dt} \exp(-\alpha t - \theta t^2/2)\right) \exp(-\mu t - \theta t^2/2) \\ &= \int_x^\infty (\alpha + \theta t) \exp(-\alpha t - \mu t - \theta t^2) dt \end{aligned}$$

Thus, two different joint densities lead to the same observable survival functions, so the joint distribution is nonidentifiable.

Here is an example showing that we may have dependent censoring and failure times, but still end up with noninformative censoring:

Example 3.2.2. Dependent failure and censoring can be noninformative

Let Y_1, Y_2 and Y_{12} be exponentially distributed with rates $\alpha_1, \alpha_2, \alpha_{12}$, respectively. Let $X = Y_1 \wedge Y_{12}$ and $C = Y_2 \wedge Y_{12}$. The survival function $P_{\alpha_1, \alpha_2, \alpha_{12}}(X > x, C > c) = P(Y_1 > x, Y_2 > c, Y_{12} > x \vee c) = e^{-\alpha_1 x - \alpha_2 c - \alpha_{12} x \vee c}$. Then marginally X is exponential with rate $\alpha_1 + \alpha_{12}$, which is also equal to its hazard function. In order for noninformative censoring to hold, we need to check Equation (3.1), or that

$$\alpha_1 + \alpha_{12} = \lim_{\Delta t \searrow 0} \frac{1}{\Delta t} \mathbb{P}_{\alpha_1, \alpha_2, \alpha_{12}}(t \leq X < t + \Delta t \mid X \geq t, C \geq t) \quad (3.4)$$

Because $t + \Delta t \vee t = t + \Delta t$ as $\Delta t > 0$,

$$\lim_{\Delta t \searrow 0} \frac{e^{-\alpha_1 t - \alpha_2 t - \alpha_{12} t} - e^{-(\alpha_1 + \alpha_{12})(t + \Delta t) - \alpha_2 t}}{\Delta t} \quad (3.5)$$

which just equals $e^{-\alpha t} - \frac{d}{ds} e^{-(\alpha_1 + \alpha_{12})s} \big|_{s=t}$ or $(\alpha_1 + \alpha_{12})e^{-\alpha_1 t - \alpha_2 t - \alpha_{12} t}$. Then

$$\lim_{\Delta t \searrow 0} \frac{1}{\Delta t} \mathbb{P}_{\alpha_1, \alpha_2, \alpha_{12}}(t \leq X < t + \Delta t \mid X \geq t, C \geq t) = \frac{(\alpha_1 + \alpha_{12})e^{-\alpha_1 t - \alpha_2 t - \alpha_{12} t}}{e^{-\alpha_1 t - \alpha_2 t - \alpha_{12} t}} \quad (3.6)$$

$$= \alpha_1 + \alpha_{12} \quad (3.7)$$

So in this case, while X and C are dependent, we still have noninformative censoring.

The benefit of noninformative censoring is that we can ignore the censoring random variables when constructing the likelihood for the survival random variables.

3.2.1 Reasons for informative censoring

A simple hypothetical situation with informative censoring would be one in which sick patients are lost to follow-up.

3.3 Truncation

While censoring can be seen as partial information about an observation, truncation deals with exact observations of selected units. The simplest example of truncation is when measurements are made using an instrument with a lower limit of detection. Imagine using a microscope to measure the diameter of cells on a plate that has a lower limit of detection of 5 microns. If interest lies in inferring the population mean diameter of the cells, one must take into account the fact that only cells with diameters of greater than 5 micros can be seen with the microscope.

Failure to take truncation into account can be a source of bias in inference.

$$\begin{aligned}\mathbb{E}[X_i] &= \mathbb{E}[X_i | X_i \geq V] P(X_i \geq V) + \mathbb{E}[X_i | X_i < V] P(X_i < V) \\ &= \mathbb{E}[X_i | X_i \geq V] + P(X_i < V)(\mathbb{E}[X_i | X_i < V] - \mathbb{E}[X_i | X_i \geq V]) \\ &\leq \mathbb{E}[X_i | X_i \geq V]\end{aligned}$$

The last line follows because $(\mathbb{E}[X_i | X_i < V] - \mathbb{E}[X_i | X_i \geq V]) \leq 0$. Using an estimator for $\mathbb{E}[X_i | X_i \geq V]$ when the target of inference in $\mathbb{E}[X_i]$ would result in positive bias. Of course, when the estimator instead estimates $\mathbb{E}[X_i | X_i < V]$ the bias would be negative. Depending on the value of V and the distribution of X_i , the bias can be severe.

For example, suppose a researcher is interested in learning about the impact of medication refills on the lifespans of patients. The researcher has access to a database in which they select patients who refilled medications at least once. The researcher subsequently selects a control group that is perfectly matched to the medication refill group, and upon analyzing the data, the analyst discovers that refilling prescription medication leads to longer lifespans. What is wrong with this analysis?

The observations in this example can be said to be left-truncated, because the researcher conditions the observations in the treatment group on having a lifespan long enough to fill a medication.

Formally, we say that the density for a truncated observation is conditioned on the probability of the observation lying in the truncated region.

- If a researcher selects $\mathbb{1}(X_i \geq V)$ we say the data are left-truncated, and $f_{X_i}(x; \eta) = \frac{-\frac{d}{dx} S_{X_i}(x; \eta)}{S_{X_i}(v; \eta)}$

- If a researcher selects $\mathbb{1}(X_i \leq U)$ we say the data are right-truncated, and $f_{X_i}(x; \eta) = \frac{-\frac{d}{dx}S_{X_i}(x; \eta)}{1-S_{X_i}(u; \eta)}$
- If a researcher selects $\mathbb{1}(V \leq X_i \leq U)$ we say the data are interval-truncated, and $f_{X_i}(x; \eta) = \frac{-\frac{d}{dx}S_{X_i}(x; \eta)}{S_{X_i}(v; \eta)-S_{X_i}(u; \eta)}$

3.4 Likelihood construction

We now turn to how to construct likelihoods in each of the prior scenarios, under censored or truncated data. As a reminder:

- Let X_i be the time to failure, or time to event for individual i .
- Let C_i be the time to censoring. It may be helpful to think about C_i as the time to investigator measurement.
- Let $\delta_i = \mathbb{1}(X_i \leq C_i)$.
- Let $T_i = \min(X_i, C_i)$.

When $\delta_i = 1$, we observe $T_i = X_i$; this is the event that $\{X_i = T_i, C_i \geq X_i\}$. When $\delta_i = 0$, we observe $T_i = C_i$; this is the event that $\{C_i = T_i, C_i < X_i\}$. Let the joint distribution of X_i, C_i be written as $P_\theta(X > x, C > c)$, and further let $\theta = (\eta, \phi)$ such that $P_\theta(X > x, C > c) = P_\eta(X > x)P_\phi(C > c \mid X > x)$. We showed in Chapter 2 that the likelihood corresponding to the random variables $T_i, \delta_i, f_{T_i, \delta_i}(t, \delta; \theta)$, can be written in terms of partial derivatives of the joint density function when X_i and C_i are absolutely continuous random variables.

$$f_{T_i, \delta_i}(t, \delta; \theta) = \left(-\frac{\partial}{\partial u} P_\theta(X \geq u, C \geq t) \mid_{u=t} \right)^\delta \left(-\frac{\partial}{\partial u} P_\theta(X \geq t, C \geq u) \mid_{u=t} \right)^{1-\delta}$$

Let's rewrite the partial derivatives in terms of their limits:

$$f_{T_i, \delta_i}(t, \delta; \theta) = \left(\lim_{\Delta t \searrow 0} \frac{1}{\Delta t} P_\theta(t \leq X < t + \Delta t, C \geq t) \right)^\delta \left(\lim_{\Delta t \searrow 0} \frac{1}{\Delta t} P_\theta(X \geq t, t \leq C < t + \Delta t) \right)^{1-\delta}$$

We can factorize the distribution function:

$$\begin{aligned} f_{T_i, \delta_i}(t, \delta; \theta) &= \left(\lim_{\Delta t \searrow 0} \frac{1}{\Delta t} P_\eta(t \leq X < t + \Delta t \mid X \geq t) P_\theta(C \geq t \mid t \leq X < t + \Delta t) P_\eta(X \geq t) \right)^\delta \\ &\quad \times \left(\lim_{\Delta t \searrow 0} \frac{1}{\Delta t} P_\phi(t \leq C < t + \Delta t \mid X \geq t) P_\eta(X \geq t) \right)^{1-\delta} \end{aligned}$$

and rearranging and subbing in $\lambda_\eta(t)$ for the hazard function:

$$f_{T_i, \delta_i}(t, \delta; \theta) = (\lambda_\eta(t))^\delta P_\eta(X \geq t) P_\theta(C \geq t \mid t \leq X < t + \Delta t)^\delta \left(\lim_{\Delta t \searrow 0} \frac{1}{\Delta t} P_\theta(t \leq C < t + \Delta t \mid X \geq t) \right)^{1-\delta}$$

Assuming that $P_\theta(C_i \geq t \mid X_i = x) = P_\phi(C_i \geq t)$ leads to the following

$$f_{T_i, \delta_i}(t, \delta; \theta) = (\lambda_\eta(t))^\delta P_\eta(X \geq t) P_\phi(C \geq t)^\delta \left(\lim_{\Delta t \searrow 0} \frac{1}{\Delta t} P_\phi(t \leq C < t + \Delta t) \right)^{1-\delta}$$

This means that we can factorize the joint density:

$$f_{T_i, \delta_i}(t, \delta; \theta) = f_{X_i, \delta_i}(t, \delta; \eta) f_{C_i, \delta_i}(t, \delta; \phi).$$

Thus, noninformative censoring and parameter separability yield a separable joint density. This means that when we want to do maximum likelihood for survival data, we can *ignore* the model for the censoring times, $f_{C_i, \delta_i}(t, \delta; \phi)$, and focus on only the model for the failure times:

$$f_{X_i, \delta_i}(t, \delta; \eta) = \lambda_{X_i}(t)^\delta P_\eta(X \geq t).$$

We can write this expression fully in terms of the hazard function by recalling Equation (2.3):

$$f_{X_i, \delta_i}(t, \delta; \eta) = \lambda_{X_i}(t)^\delta \exp\left(-\int_0^t \lambda_{X_i}(u) du\right). \quad (3.8)$$

Example 3.4.1. MLE for exponential survival time Let $X_i \stackrel{\text{iid}}{\sim} \text{Exp}(\alpha)$ and assume we have independent censoring ($X_i \perp C_i$), the parameters for the censoring process are separable from α , and that C_i are iid such that $\mathbb{E}[C_i] < \infty$. Then our observed data are $T_i = \min(X_i, C_i)$ and $\delta_i = \mathbb{1}(X_i \leq C_i)$. According to Equation (4.1) we can write the likelihood as

$$\begin{aligned} f_\alpha(t_1, \dots, t_n, \delta_1, \dots, \delta_n) &= \prod_{i=1}^n \alpha^{\delta_i} \exp(-\sum_{i=1}^n \int_0^{t_i} \alpha du) \\ &= \alpha^{\sum_{i=1}^n \delta_i} \exp(-\alpha \sum_{i=1}^n t_i) \end{aligned}$$

The log-likelihood is

$$\log(f_\alpha(t_1, \dots, t_n, \delta_1, \dots, \delta_n)) = \log(\alpha) \sum_{i=1}^n \delta_i - \alpha \sum_{i=1}^n t_i$$

which has the maximizer

$$\hat{\alpha} = \frac{\sum_{i=1}^n \delta_i}{\sum_{i=1}^n t_i}.$$

Let's show that this converges a.s. to α as $n \rightarrow \infty$. We can rewrite $\frac{\sum_{i=1}^n \delta_i}{\sum_{i=1}^n t_i}$ as

$$\frac{\frac{1}{n} \sum_{i=1}^n \mathbb{1}(X_i \leq C_i)}{\frac{1}{n} \sum_{i=1}^n X_i \mathbb{1}(X_i \leq C_i) + C_i \mathbb{1}(X_i > C_i)}$$

The top and bottom expressions converge a.s. by Kolmogorov's Strong Law of Large Numbers to

$$\begin{aligned} \frac{1}{n} \sum_{i=1}^n \mathbb{1}(X_i \leq C_i) &\xrightarrow{\text{a.s.}} \mathbb{E}_{(X_i, C_i)} [\mathbb{1}(X_i \leq C_i)] \\ \frac{1}{n} \sum_{i=1}^n X_i \mathbb{1}(X_i \leq C_i) + C_i \mathbb{1}(X_i > C_i) &\xrightarrow{\text{a.s.}} \mathbb{E}_{(X_i, C_i)} [X_i \mathbb{1}(X_i \leq C_i) + C_i \mathbb{1}(X_i > C_i)] \end{aligned}$$

We can evaluate the top expression using the tower property of expectation:

$$\begin{aligned}\mathbb{E}_{(X_i, C_i)} [\mathbb{1}(X_i \leq C_i)] &= \mathbb{E}_{C_i} [\mathbb{E}_{X_i|C_i} [\mathbb{1}(X_i \leq c) \mid C_i = c]] \\ &= \mathbb{E}_{C_i} [1 - e^{-\alpha C_i}]\end{aligned}$$

where the second line follows from the independent censoring condition. The bottom expression becomes:

$$\begin{aligned}\mathbb{E}_{(X_i, C_i)} [X_i \mathbb{1}(X_i \leq C_i) + C_i \mathbb{1}(X_i > C_i)] &= \mathbb{E}_{C_i} [\mathbb{E}_{X_i|C_i} [X_i \mathbb{1}(X_i \leq c) \mid C_i = c]] \\ &\quad + \mathbb{E}_{C_i} [\mathbb{E}_{X_i|C_i} [c \mathbb{1}(X_i > c) \mid C_i = c]] \\ &= \mathbb{E}_{C_i} \left[\frac{1}{\alpha} (1 - (1 + \alpha C_i) e^{-\alpha C_i}) \right] + \mathbb{E}_{C_i} [C_i e^{-\alpha C_i}] \\ &= \frac{1}{\alpha} \mathbb{E}_{C_i} [1 - e^{-\alpha C_i}]\end{aligned}$$

Thus

$$\frac{\sum_{i=1}^n \delta_i}{\sum_{i=1}^n t_i} \xrightarrow{\text{a.s.}} \alpha$$

To show that $\int_0^c x \alpha e^{-\alpha x} dx = \frac{1}{\alpha} (1 - (1 + \alpha c) e^{-\alpha c})$, we can use the trick of differentiating under the integral sign.

$$\begin{aligned}\alpha \int_0^c x e^{-\alpha x} dx &= \alpha \int_0^c -\frac{d}{d\alpha} e^{-\alpha x} dx \\ &= \alpha \left(-\frac{d}{d\alpha} \right) \int_0^c e^{-\alpha x} dx \\ &= \alpha \left(-\frac{d}{d\alpha} \right) \frac{1}{\alpha} (1 - e^{-\alpha c}) \\ &= \alpha \left(\frac{1 - (1 + \alpha c) e^{-\alpha c}}{\alpha^2} \right)\end{aligned}$$

Chapter 4

Nonparametric estimator of survival function

4.1 Derivation of Nelson-Aalen and Kaplan-Meier estimators

When we have $(X_i, C_i) \stackrel{\text{iid}}{\sim} F$ such that noninformative censoring and parameter separability hold, we showed in Equation (3.8) that we can write the likelihood for the survival process:

$$f_{\eta}(t_1, \dots, t_n, \delta_1, \dots, \delta_n) = \prod_{i=1}^n \lambda_{\eta}(t_i)^{\delta_i} \exp \left(- \int_0^{t_i} \lambda_{\eta}(u) du \right).$$

This can again be simplified by collecting terms inside the exponential:

$$f_{\eta}(t_1, \dots, t_n, \delta_1, \dots, \delta_n) = \left(\prod_{i=1}^n \lambda_{\eta}(t_i)^{\delta_i} \right) \exp \left(- \sum_{i=1}^n \int_0^{t_i} \lambda_{\eta}(u) du \right). \quad (4.1)$$

Let's make a slight change to how we write the survival function. Define the indicator function $Y(u)$ to be

$$Y_i(u) = \mathbb{1}(t_i \geq u).$$

This function is left-continuous, with right-hand limits, an example of which is shown in Figure 4.1:

This allows us to rewrite our likelihood as follows:

$$f_{\eta}(t_1, \dots, t_n, \delta_1, \dots, \delta_n) = \left(\prod_{i=1}^n \lambda_{\eta}(t_i)^{\delta_i} \right) \exp \left(- \sum_{i=1}^n \int_0^{\infty} Y_i(u) \lambda_{\eta}(u) du \right) \quad (4.2)$$

$$= \left(\prod_{i=1}^n \lambda_{\eta}(t_i)^{\delta_i} \right) \exp \left(- \int_0^{\infty} \lambda_{\eta}(u) \sum_{i=1}^n Y_i(u) du \right) \quad (4.3)$$

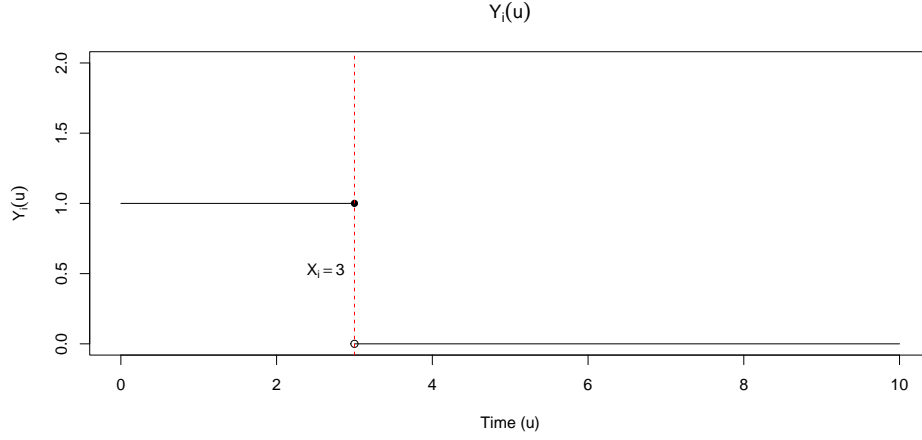


Figure 4.1: Example plot of an at-risk function

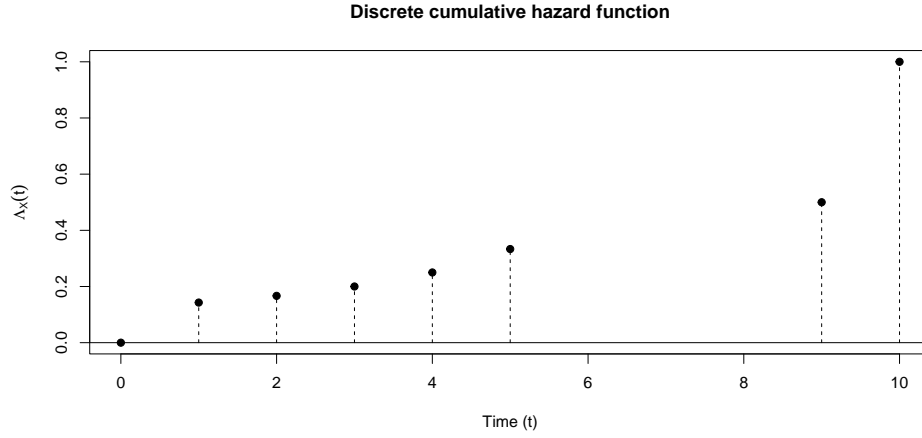


Figure 4.2: Example plot of a discrete hazard function

For notational convenience, we'll define the function $\bar{Y}(u)$ as:

$$\bar{Y}(u) = \sum_{i=1}^n Y_i(u).$$

Then our likelihood is:

$$f_{\eta}(t_1, \dots, t_n, \delta_1, \dots, \delta_n) = \left(\prod_{i=1}^n \lambda_{\eta}(t_i)^{\delta_i} \right) \exp \left(- \int_0^{\infty} \lambda_{\eta}(u) \bar{Y}(u) du \right) \quad (4.4)$$

We can consider a nonparametric model for the hazard, estimating λ at each t_i as a separate parameter. An example of this is shown in Figure 4.2, which corresponds to the discrete survival function in Figure 2.1. In order to evaluate the integral

$$\int_0^{\infty} \lambda(u) \bar{Y}(u) du,$$

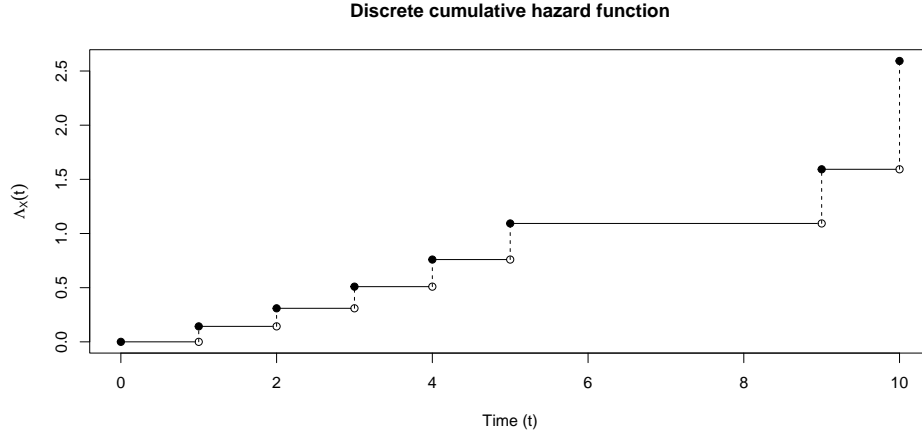


Figure 4.3: Example plot of a discrete cumulative hazard function

note that we can rewrite $\lambda(t_i)$ as

$$\lambda(t_i) = \Lambda(t_i) - \Lambda(t_i-),$$

where $\Lambda(t)$ is the cumulative hazard function. We'll write as $\lambda(u)$ as $d\Lambda(u)$. Finally, recall that because $S(t)$ is right-continuous, $\Lambda(t)$ is also right-continuous. We'll also need a bit of integration theory from Lebesgue-Stieltjes integrals. Suppose that G is a right-continuous, monotone function on $[0, \infty)$ with countably many discontinuities at a_i , and let $dG(a_i) = G(a_i) - G(a_i-)$. Then for a measurable function F on $[0, \infty)$, the integral over a set B

$$\int_B F(x) dG(x) = \sum_{i|a_i \in B} F(a_i) dG(a_i).$$

Using these results, the integral can be evaluated to

$$\int_0^\infty (\bar{Y}(u)) d\Lambda(u) du = \sum_{j=1}^n \lambda(t_j) \bar{Y}(t_j)$$

Let's take the log of the expression to get a log-likelihood:

$$\log f_\eta(t_1, \dots, t_n, \delta_1, \dots, \delta_n) = \sum_{i=1}^n \delta_i \log(\lambda_\eta(t_i)) - \sum_{j=1}^n \lambda_\eta(t_j) \bar{Y}(t_j) \quad (4.5)$$

Taking the gradient with respect to $\lambda_\eta(t_i)$ gives

$$\nabla \log f_\eta(t_1, \dots, t_n, \delta_1, \dots, \delta_n) = \frac{\delta_i}{\lambda_\eta(t_i)} - \bar{Y}(t_i). \quad (4.6)$$

Note that the Hessian is also diagonal, which implies asymptotic independence of $\lambda(t_i)$. This is solved at

$$\hat{\lambda}_\eta(t_i) = \frac{\delta_i}{\bar{Y}(t_i)} \quad (4.7)$$

This gives an expression for $\Lambda(t)$:

$$\Lambda^{\text{NA}}(t) = \sum_{i|\delta_i=1, t_i \leq t} \frac{1}{\bar{Y}(t_i)} \quad (4.8)$$

This also gives an expression for $S(t)$:

$$S^{\text{KM}}(t) = \prod_{i|\delta_i=1, t_i \leq t} \left(1 - \frac{1}{\bar{Y}(t_i)}\right). \quad (4.9)$$

This is also known as the **Kaplan-Meier estimator**. An alternative expression is:

$$S^{\text{NA}}(t) = \exp\left(-\sum_{i|\delta_i=1, t_i \leq t} \frac{1}{\bar{Y}(t_i)}\right) \quad (4.10)$$

We can show that the cumulative hazard as implied by Equation (4.9) is asymptotically equivalent to Equation (4.8). Given Equation (2.9)

$$\Lambda^{\text{KM}} = -\log\left(\prod_{i|\delta_i=1, t_i \leq t} \left(1 - \frac{1}{\bar{Y}(t_i)}\right)\right) \quad (4.11)$$

$$= -\sum_{i|\delta_i=1, t_i \leq t} \log\left(1 - \frac{1}{\bar{Y}(t_i)}\right) \quad (4.12)$$

$$\approx \sum_{i|\delta_i=1, t_i \leq t} \frac{1}{\bar{Y}(t_i)} \quad (4.13)$$

where the last line follows from the Taylor approximation of $\log(1-x) \approx -x$ when $x \approx 0$.

4.1.1 Kaplan-Meier estimator standard error

In order to get the standard errors for the Kaplan-Meier estimator, we'll use a Taylor expansion:

$$\log(S^{\text{KM}}(t)) \approx \log(S(t)) + \frac{1}{S(t)}(S^{\text{KM}}(t) - S(t)) \quad (4.14)$$

which leads to

$$\text{Var}(\log(S^{\text{KM}}(t))) = \frac{1}{S(t)^2} \text{Var}(S^{\text{KM}}(t))$$

or

$$\text{Var}(S^{\text{KM}}(t)) = \text{Var}(\log(S^{\text{KM}}(t))) S(t)^2.$$

We use the plug-in estimator for $S(t)$ here, so we get:

$$\text{Var}(S^{\text{KM}}(t)) = \text{Var}(\log(S^{\text{KM}}(t))) (S^{\text{KM}}(t))^2.$$

Now we need an expression for $\text{Var}(\log(S^{\text{KM}}(t)))$. First we write the log of the KM estimator:

$$\log \hat{S}^{\text{KM}}(t) = \sum_{i|t_i \leq t} \log(1 - \hat{\lambda}(t_i)). \quad (4.15)$$

First we find the Taylor expansion for each term, which is justified by the fact that $(1 - \hat{\lambda}(t_i)) \approx (1 - \lambda(t_i))$ for large samples:

$$\log(1 - \hat{\lambda}(t_i)) \approx \log(1 - \lambda(t_i)) - \frac{1}{1 - \lambda(t_i)} (\hat{\lambda}(t_i) - \lambda(t_i)) \quad (4.16)$$

Then

$$\text{Var}(\log(1 - \hat{\lambda}(t_i))) \approx \frac{1}{(1 - \lambda(t_i))^2} \text{Var}(\hat{\lambda}(t_i))$$

We can estimate the $\text{Var}(\hat{\lambda}(t_i))$ as:

$$\text{Var}(\hat{\lambda}(t_i)) = \text{Var}(\delta_i) / \bar{Y}^2(t_i)$$

Treating δ_i as a binomial random variable with $\bar{Y}(t_i)$ number of trials:

$$\delta_i \sim \text{Binomial}(\bar{Y}(t_i), p_i)$$

The variance of δ_i is $p_i(1 - p_i)\bar{Y}(t_i)$. Using $\hat{\lambda}(t_i)$ as a plug-in estimator for p_i as $\hat{\lambda}(t_i)$, this gives:

$$\text{Var}(\delta_i) = \hat{\lambda}(t_i)(1 - \hat{\lambda}(t_i))\bar{Y}(t_i)$$

Putting this together with the $\bar{Y}^2(t_i)$ in the denominator gives the following estimate for the variance of $\hat{\lambda}(t_i)$:

$$\frac{\hat{\lambda}(t_i)(1 - \hat{\lambda}(t_i))}{\bar{Y}(t_i)}.$$

Finally using the plug-in estimator for $(1 - \lambda(t_i))^2$ in the denominator of the Taylor expansion formula gives:

$$\text{Var}(\log(1 - \hat{\lambda}(t_i))) \approx \frac{1}{(1 - \hat{\lambda}(t_i))^2} \frac{\hat{\lambda}(t_i)(1 - \hat{\lambda}(t_i))}{\bar{Y}(t_i)} \quad (4.17)$$

$$\approx \frac{\hat{\lambda}(t_i)}{\bar{Y}(t_i)(1 - \hat{\lambda}(t_i))} \quad (4.18)$$

$$\approx \frac{\delta_i}{\bar{Y}(t_i)(\bar{Y}(t_i) - \hat{\lambda}(t_i))} \quad (4.19)$$

Putting this all together along with the fact that $\lambda(t_i) \stackrel{\text{asympt}}{\parallel} \lambda(t_j)$, yields what is known as **Greenwood's formula**:

$$\text{Var}(S^{\text{KM}}(t)) = (S^{\text{KM}}(t))^2 \sum_{i|\delta_i=1, t_i \leq t} \frac{\delta_i}{\bar{Y}(t_i)(\bar{Y}(t_i) - \delta_i)}.$$

4.2 Confidence intervals

If we wanted to construct asymptotic, point-wise confidence intervals for the KM estimator, we can go about it in several ways. The most straightforward way to compute confidence intervals is to directly use the estimated survival function at t_0 and the standard error estimator from Greenwood's formula. Let $\hat{\sigma}(t)$ be

$$\sqrt{\sum_{i|d_i=1, t_i \leq t} \frac{d_i}{\bar{Y}(t_i)(\bar{Y}(t_i) - d_i)}}.$$

Then our confidence interval, C^{KM} , is

$$C^{\text{KM}} = (\hat{S}^{\text{KM}}(t_0) - z_{1-\alpha/2} \hat{\sigma} \hat{S}^{\text{KM}}(t_0), \hat{S}^{\text{KM}}(t_0) + z_{1-\alpha/2} \hat{\sigma} \hat{S}^{\text{KM}}(t_0))$$

The issue with this confidence interval is that it is not guaranteed to be greater than zero or less than 1, so we may have nonsensical results for upper and lower bounds. A solution is to build a confidence set for a suitably transformed Kaplan Meier estimator, and use the inverse transformation to enforce the natural $[0, 1]$ bounds. One option is to use the logit transformation, another is to use the log-log transformation.

We'll walk through the log-log transformation:

Note that we have the following result:

$$\text{Var}(\log(\hat{S}^{\text{KM}}(t))) = \frac{1}{S(t)^2} \text{Var}(\hat{S}^{\text{KM}}(t)) \quad (4.20)$$

$$= \sum_{i|d_i=1, t_i \leq t} \frac{d_i}{\bar{Y}(t_i)(\bar{Y}(t_i) - d_i)}. \quad (4.21)$$

Then

$$\log(-\log(\hat{S}^{\text{KM}}(t))) \approx \log(-\log(S(t))) - \frac{1}{\log(S(t))} (\log(\hat{S}^{\text{KM}}(t)) - \log(S(t)))$$

So

$$\text{Var}(\log(-\log(\hat{S}^{\text{KM}}(t)))) \approx \frac{1}{\log(S(t))^2} \text{Var}(\log(\hat{S}^{\text{KM}}(t)))$$

or

$$\text{SE}(\log(-\log(\hat{S}^{\text{KM}}(t)))) \approx \frac{1}{|\log(S(t))|} \hat{\sigma}(t)$$

Let $u = \log(-\log S(t))$, $\hat{u} = \log(-\log(\hat{S}^{\text{KM}}(t)))$, and $\hat{\sigma}_u = \text{SE}(\log(-\log(\hat{S}^{\text{KM}}(t))))$. Then

$$\hat{S}^{\text{KM}}(t) = \exp(-e^{\hat{u}}).$$

Note that $\exp(-e^u)$ is a monotone decreasing function of its input, u . This means that for a set $[a, b]$

$$a \leq u \leq b \implies \exp(-e^a) \geq \exp(-e^u) \geq \exp(-e^b).$$

We'll take it as a given that asymptotically,

$$\frac{\hat{u} - u}{\hat{\sigma}_u} \xrightarrow{d} \mathcal{N}(0, 1).$$

Then we can derive an alternative asymptotic confidence interval for the Kaplan-Meier estimator of survival at time t_0 by transforming a confidence interval for u . Let $z_{1-\alpha/2}$ be the $1 - \alpha/2$ quantile of a standard normal distribution with CDF Φ , or

$$z_{1-\alpha/2} = \Phi^{-1}(1 - \alpha/2).$$

$$\begin{aligned} P(-z_{1-\alpha/2} \leq \frac{\hat{u} - u}{\hat{\sigma}_u} \leq z_{1-\alpha/2}) &= P(\hat{u} - \hat{\sigma}_u z_{1-\alpha/2} \leq u \leq \hat{u} + \hat{\sigma}_u z_{1-\alpha/2}) \\ &= P(\exp(-e^{\hat{u} - \hat{\sigma}_u z_{1-\alpha/2}}) \geq \exp(-e^u) \geq \exp(-e^{\hat{u} + \hat{\sigma}_u z_{1-\alpha/2}})) \\ &= P(\exp(-e^{\hat{u}} e^{-\hat{\sigma}_u z_{1-\alpha/2}}) \geq \exp(-e^u) \geq \exp(-e^{\hat{u}} e^{\hat{\sigma}_u z_{1-\alpha/2}})) \\ &= P(\exp(-e^{\hat{u}}) e^{-\hat{\sigma}_u z_{1-\alpha/2}} \geq \exp(-e^u) \geq \exp(-e^{\hat{u}}) e^{\hat{\sigma}_u z_{1-\alpha/2}}) \\ &= P((\hat{S}^{\text{KM}}(t))^{e^{-\text{SE}(\log(-\log(\hat{S}^{\text{KM}}(t))))z_{1-\alpha/2}}} \geq S(t) \\ &\quad \geq (\hat{S}^{\text{KM}}(t))^{e^{\text{SE}(\log(-\log(\hat{S}^{\text{KM}}(t))))z_{1-\alpha/2}}}). \end{aligned}$$

So

$$P\left(S(t) \in \left((\hat{S}^{\text{KM}}(t))^{e^{\text{SE}(\log(-\log(\hat{S}^{\text{KM}}(t))))z_{1-\alpha/2}}}, (\hat{S}^{\text{KM}}(t))^{e^{-\text{SE}(\log(-\log(\hat{S}^{\text{KM}}(t))))z_{1-\alpha/2}}}\right)\right) \stackrel{\text{asympt.}}{=} 1 - \alpha \quad (4.22)$$

4.2.1 Handling ties in the Nelson-Aalen estimator

We had assumed that no two events could occur at the same time, but for most real datasets this isn't realistic. A distinction must be made between a) assuming that ties are present in the data because, despite the true events happening in continuous time and thus no two events exactly coincide, the data have been rounded such that this exact ordering of events is lost, or b) that the true events happen in discrete time, and so there are truly events that co-occur.

In the continuous time scenario, Aalen et al. 2008 suggests using a modified estimator for hazard at time t_i when there are multiple $\delta_i = 1$. Let d_i be the number of events observed at time t_i . Then the proposed estimator for $\hat{\lambda}(t_i)$ is:

$$\hat{\lambda}(t_i) = \sum_{j=0}^{d_i-1} \frac{1}{\overline{Y}(t_i) - j} \quad (4.23)$$

In discrete time the proposal is to use:

$$\hat{\lambda}(t_i) = \frac{d_i}{\overline{Y}(t_i)} \quad (4.24)$$

4.2.2 Handling ties in the Kaplan-Meier estimator

It turns out, after some algebra, that using either Equation (4.23) or Equation (4.24) results in the following tie-corrected estimator for the KM estimator:

$$\hat{S}^{\text{KM}}(t) = \prod_{i|d_i \geq 1, t_i \leq t} \left(1 - \frac{d_i}{\overline{Y}(t_i)}\right) \quad (4.25)$$

Greenwood's formula is then

$$\text{Var}(S^{\text{KM}}(t)) = (S^{\text{KM}}(t))^2 \sum_{i|d_i=1, t_i \leq t} \frac{d_i}{\overline{Y}(t_i)(\overline{Y}(t_i) - d_i)}.$$

This is the more commonly known form.

4.3 Nonparametric tests

Now that we've derived the nonparametric estimator for the cumulative hazard function, $\Lambda^{\text{NA}}(t) = \sum_{i|\delta_i=1, t_i \leq t} \frac{1}{\overline{Y}(t_i)}$, we may be interested in testing the hypothesis that two populations have different cumulative hazard functions.

Intuitively it would make sense to compare the difference between the two cumulative hazard functions up to some τ :

$$\Lambda_1^{\text{NA}}(\tau) - \Lambda_2^{\text{NA}}(\tau) \quad (4.26)$$

and if this difference were large relative to the standard error under the null hypothesis, reject the null in favor of the alternative.

Let's formalize this a bit more. If the null hypothesis is:

$$H_0 : \lambda_1(t) = \lambda_2(t) \forall t \in [0, \tau]$$

then we can represent this common hazard function at $\lambda(t)$. Under the null, the nonparametric estimator combines all of the event times into one dataset and estimates $\hat{\lambda}(t)$. Let $\bar{Y}(t) = \bar{Y}_1(t) + \bar{Y}_2(t)$ be the total population at risk between the two samples. Let there be n_1 and n_2 samples in each respective study set. Let $t_1 \leq t_2 \leq \dots \leq t_{n_1+n_2}$ be the total combined set of event times. Let d_i be the total number of failures occurring at time t_i , and let d_{ij} be the total number of failures occurring at time t_i for sample j . Note that this could be zero.

Then the Nelson-Aalen estimator, assuming discrete time ties, for the cumulative hazard under the null is

$$\hat{\Lambda}^{\text{NA}}(\tau) = \sum_{i=1|t_i \leq \tau}^{n_1+n_2} \frac{d_i}{\bar{Y}(t_i)} \quad (4.27)$$

Then let the Nelson-Aalen estimator for the j -th cumulative hazard be

$$\hat{\Lambda}^{\text{NA}}(\tau) = \sum_{i=1|t_i \leq \tau}^{n_1+n_2} \frac{d_{ij}}{\bar{Y}_j(t_i)} \quad (4.28)$$

Given the common index over t_i we can compare the two sums more easily:

$$Z_j(\tau) = \sum_{i=1|t_i \leq \tau}^{n_1+n_2} \left(\frac{d_{ij}}{\bar{Y}_j(t_i)} - \frac{d_i}{\bar{Y}(t_i)} \right). \quad (4.29)$$

We can weight the comparisons differently by adding a weighting factor that is a function of t and j :

$$Z_j(\tau) = \sum_{i=1|t_i \leq \tau}^{n_1+n_2} W_j(t_i) \left(\frac{d_{ij}}{\bar{Y}_j(t_i)} - \frac{d_i}{\bar{Y}(t_i)} \right). \quad (4.30)$$

Crucially, this weighting function has the property that $W_j(t_i) = 0$ when $\bar{Y}_j(t_i) = 0$, because the hazard rate estimator $\hat{\lambda}_j(t_i)$ is not defined in this case. Let's rewrite the statistic $Z(\tau)$ a bit differently to elucidate the statistical properties, assuming that $W_j(t_i) = W(t_i) \bar{Y}_j(t_i)$, which satisfies the requirement that $W_j(t_i) = 0$ when $\bar{Y}_j(t_i) = 0$:

$$Z_j(\tau) = \sum_{i=1|t_i \leq \tau}^{n_1+n_2} W(t_i) \bar{Y}_j(t_i) \left(\frac{d_{ij}}{\bar{Y}_j(t_i)} - \frac{d_i}{\bar{Y}(t_i)} \right) \quad (4.31)$$

$$= \sum_{i=1|t_i \leq \tau}^{n_1+n_2} W(t_i) \left(d_{ij} - d_i \frac{\bar{Y}_j(t_i)}{\bar{Y}(t_i)} \right) \quad (4.32)$$

Now, conditional on $d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)$, d_{ij} are distributed as hypergeometric random variables. Recall the definition of a hypergeometric random variable: It defines the distribution of successes (in our case this is failures) in a sample size of n from a finite population of size N where the total number of successes is K , with mean $n\frac{K}{N}$. The analogy to our scenario is d_{ij} is the number of failures in a samples of size $\bar{Y}_j(t_i)$ in a population size $\bar{Y}(t_i)$ where the total number of failures is d_i .

$$p(d_{ij} = k \mid d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)) = \frac{\binom{d_i}{k} \binom{\bar{Y}(t_i) - d_i}{\bar{Y}_j(t_i) - k}}{\binom{\bar{Y}(t_i)}{\bar{Y}_j(t_i)}}.$$

Then

$$\mathbb{E}[d_{ij} \mid d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)] = d_i \frac{\bar{Y}_j(t_i)}{\bar{Y}(t_i)}$$

For notational convenience, let's call $A_{ij} = d_{ij} - d_i \frac{\bar{Y}_j(t_i)}{\bar{Y}(t_i)}$. Under the null hypothesis, the mean of $Z_j(\tau)$ is zero, because $\mathbb{E}[A_{ij} \mid d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)] = 0$ so

$$\mathbb{E}[A_{ij}] = \mathbb{E}_{d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)} [\mathbb{E}[A_{ij} \mid d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)]] = 0.$$

We can also compute the variance using our result.

$$\text{Var}(Z_j(\tau)) = \sum_i W(t_i)^2 \text{Var}(A_{ij}) + 2 \sum_{i < k} W(t_i) W(t_j) \text{Cov}(A_{ij}, A_{kj})$$

Given the hypergeometric distribution, we can read off the variance as

$$\text{Var}(A_{ij}) = d_i \frac{\bar{Y}_j(t_i)}{\bar{Y}(t_i)} \left(1 - \frac{\bar{Y}_j(t_i)}{\bar{Y}(t_i)} \right) \frac{\bar{Y}(t_i) - d_i}{\bar{Y}(t_i) - 1}$$

Now let's compute $\text{Cov}(A_{ij}, A_{kj})$, noting that $i < k$. We know that $\mathbb{E}[A_{ij}] = 0$, so we just need to compute $\mathbb{E}[A_{ij} A_{kj}]$. We can use the tower property of expectation. First we need to define something called the history, or the *filtration*, of the process. A filtration is an increasing family of σ -algebras, $\{\mathcal{F}_l, 0 \leq l < \infty\}$ such that $\mathcal{F}_l \subset \mathcal{F}_m$ for all $l < m$. This is a way of formalizing the idea that as time progresses, information about events accrues. If an event $E \in \mathcal{F}_l$ then $\mathbb{E}[\mathbb{1}(E) \mid \mathcal{F}_l] = \mathbb{1}(E)$, because we're conditioning on the full set of information, and E is part of that information. It's analogous to saying for two random variables X, Y , $\mathbb{E}[XY \mid X] = X \mathbb{E}[Y \mid X]$. Taking this approach below, we show that the covariance is zero. Let \mathcal{F}_k be the collection of information just before t_k , which means, more formally that it is

$$\mathcal{F}_k = \sigma\{d_{i1}, d_{i2}, \bar{Y}_1(t_i), \bar{Y}_2(t_i), i < k\} \quad (4.33)$$

Then

$$\mathbb{E}[A_{ij}A_{kj}] = \mathbb{E}[\mathbb{E}[A_{ij}A_{kj} \mid \mathcal{F}_k]] \quad (4.34)$$

$$= \mathbb{E}[A_{ij}\mathbb{E}[A_{kj} \mid \mathcal{F}_k]] \quad (4.35)$$

$$= 0. \quad (4.36)$$

Where the last line follows because

$$\mathbb{E}[A_{kj} \mid \mathcal{F}_k] = \mathbb{E}_{d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)}[\mathbb{E}[A_{kj} \mid \mathcal{F}_k, d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)]] \quad (4.37)$$

$$= 0 \quad (4.38)$$

as we showed above. Thus,

$$\text{Var}(Z_j(\tau)) = \sum_i W(t_i)^2 \text{Var}(A_{ij}) \quad (4.39)$$

$$= \sum_i W(t_i)^2 \left(d_i \frac{\bar{Y}_j(t_i)}{\bar{Y}(t_i)} \left(1 - \frac{\bar{Y}_j(t_i)}{\bar{Y}(t_i)} \right) \frac{\bar{Y}(t_i) - d_i}{\bar{Y}(t_i) - 1} \right) \quad (4.40)$$

Note that, due to A_{ij} being mean zero, we have that

$$\begin{aligned} \text{Var}(A_{ij}) &= \mathbb{E}_{d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)}[\text{Var}(A_{ij} \mid d_i, \bar{Y}_j(t_i), \bar{Y}(t_i))] + \text{Var}(\mathbb{E}[A_{ij} \mid d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)]) \\ &= \mathbb{E}_{d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)}[\text{Var}(A_{ij} \mid d_i, \bar{Y}_j(t_i), \bar{Y}(t_i))] \end{aligned}$$

Then

$$\text{Var}(A_{ij}) = \mathbb{E}_{d_i, \bar{Y}_j(t_i), \bar{Y}(t_i)}[\text{Var}(A_{ij} \mid d_i, \bar{Y}_j(t_i), \bar{Y}(t_i))]$$

This means that we can construct an unbiased estimator for $\text{Var}(Z_j(\tau))$ by the following:

$$\text{Var}(\hat{Z}_j(\tau)) = \sum_i W(t_i)^2 \text{Var}(A_{ij} \mid d_i, \bar{Y}(t_i), \bar{Y}_j(t_i))$$

and

$$\begin{aligned} \mathbb{E}[\text{Var}(\hat{Z}_j(\tau))] &= \sum_i W(t_i)^2 \mathbb{E}[\text{Var}(A_{ij} \mid d_i, \bar{Y}(t_i), \bar{Y}_j(t_i))] \\ &= \sum_i W(t_i)^2 \text{Var}(A_{ij}) \\ &= \text{Var}(Z_j(\tau)) \end{aligned}$$

We won't go into the details yet, but it turns out that

$$\frac{Z_j(\tau)}{\sqrt{\text{Var}(\hat{Z}_j(\tau))}} \stackrel{\text{asympt.}}{\sim} \text{Normal}(0, 1)$$

One could use this result to define a rejection region that is calibrated under the null.

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