Introduction to Survival Analysis

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Configuring R

Functions from these packages will be used throughout this document:

```
library(conflicted) # check for conflicting function definitions
# library(printr) # inserts help-file output into markdown output
library(rmarkdown) # Convert R Markdown documents into a variety of formats.
library(pander) # format tables for markdown
library(ggplot2) # graphics
library(ggfortify) # help with graphics
library(dplyr) # manipulate data
library(tibble) # `tibble`s extend `data.frame`s
library(magrittr) # `%>%` and other additional piping tools
library(haven) # import Stata files
library(knitr) # format R output for markdown
library(tidyr) # Tools to help to create tidy data
library(plotly) # interactive graphics
library(dobson) # datasets from Dobson and Barnett 2018
library(parameters) # format model output tables for markdown
library(haven) # import Stata files
library(latex2exp) # use LaTeX in R code (for figures and tables)
library(fs) # filesystem path manipulations
library(survival) # survival analysis
library(survminer) # survival analysis graphics
library(KMsurv) # datasets from Klein and Moeschberger
library(parameters) # format model output tables for
library(webshot2) # convert interactive content to static for pdf
library(forcats) # functions for categorical variables ("factors")
```

```r
library(stringr) # functions for dealing with strings
library(lubridate) # functions for dealing with dates and times
library(broom) # Summarizes key information about statistical objects in tidy tibbles
library(broom.helpers) # Provides suite of functions to work with regression model 'broom::tidy()' t
```

Here are some R settings I use in this document:

```r
rm(list = ls()) # delete any data that's already loaded into R

conflicts_prefer(dplyr::filter)
ggplot2::theme_set(
  ggplot2::theme_bw() +
        # ggplot2::labs(col = "") +
    ggplot2::theme(
      legend.position = "bottom",
      text = ggplot2::element_text(size = 12, family = "serif")))

knitr::opts_chunk$set(message = FALSE)
options('digits' = 6)

panderOptions("big.mark", ",")
pander::panderOptions("table.emphasize.rownames", FALSE)
pander::panderOptions("table.split.table", Inf)
conflicts_prefer(dplyr::filter) # use the `filter()` function from dplyr() by default
legend_text_size = 9
run_graphs = TRUE
```

1 Overview

This chapter introduces **survival analysis** (also known as *time-to-event analysis*):

- Survival outcomes and censoring mechanisms
- Key distribution functions: PDF, CDF, survival function, inverse survival (quantile) function, hazard, and cumulative hazard
- Parametric models for survival data (exponential, Weibull)
- Nonparametric estimation: the Kaplan-Meier product-limit estimator
- The log-rank test for comparing survival curves
- The Nelson-Aalen cumulative hazard estimator
- The empirical inverse survival function

2 Time-to-event outcomes

Survival analysis is a framework for modeling *time-to-event* outcomes. It is used in:

- clinical trials, where the event is often death or recurrence of disease.
- engineering reliability analysis, where the event is failure of a device or system.
- insurance, particularly life insurance, where the event is death.

> **Note**
>
> The term *survival analysis* is a bit misleading. Survival outcomes can sometimes be analyzed using binomial models (logistic regression). *Time-to-event models* or *survival time analysis* might be a better name.

3 Time-to-event outcome distributions

3.1 Distributions of Time-to-Event Data

- The distribution of event times is asymmetric and can be long-tailed, and starts at 0 (that is, $P(T < 0) = 0$).
- The base distribution is not normal, but exponential.
- There are usually **censored** observations, which are ones in which the failure time is not observed.
- Often, these are **right-censored**, meaning that we know that the event occurred after some known time t, but we don't know the actual event time, as when a patient is still alive at the end of the study.
- Observations can also be **left-censored**, meaning we know the event has already happened at time t, or **interval-censored**, meaning that we only know that the event happened between times t_1 and t_2.
- Analysis is difficult if censoring is associated with treatment.

Definition 3.1 (Right Censoring)**. Right censoring** occurs when the observed follow-up time is less than the true event time — we know only that the event has not yet occurred by the time of last contact.

- Patients are in a clinical trial for cancer, some on a new treatment and some on standard of care.
- Some patients in each group have died by the end of the study. We know the survival time (measured for example from time of diagnosis—each person on their own clock).
- Patients still alive at the end of the study are right censored.
- Patients who are lost to follow-up or withdraw from the study may be right-censored.

Definition 3.2 (Left Censoring)**. Left censoring** occurs when the event is known to have already happened before the first observation time — we know only that the event time is less than some observed time t.

- An individual tests positive for HIV.
- If the event is infection with HIV, then we only know that it has occurred before the testing time t, so this is left censored.

Definition 3.3 (Interval Censoring)**. Interval censoring** occurs when the event is known to have occurred within a specific time interval $(t_1, t_2]$, but the exact event time is unobserved.

- If an individual has a negative HIV test at time t_1 and a positive HIV test at time t_2, then the infection event is interval censored.

4 Distribution functions for time-to-event variables

4.1 The Probability Density Function (PDF)

For a time-to-event variable T with a continuous distribution, the **probability density function** is defined as usual (see probability density function[1]).

In most time-to-event models, this density is assumed to be 0 for all $t < 0$; that is, $f(t) = 0, \forall t < 0$. In other words, the support of T is typically $[0, \infty)$.

---

[1] probability.qmd#sec-prob-dens

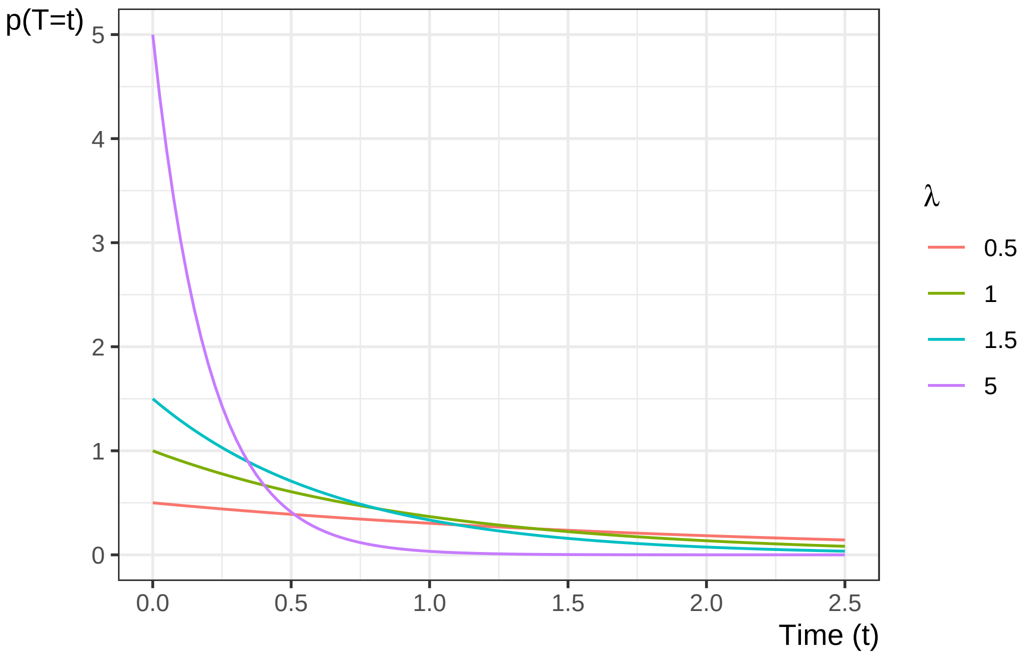
Exm

Example 4.1 (exponential distribution)**.** Recall from Epi 202: the pdf of the exponential distribution family of models is:

$$p(T = t) = 1_{t \geq 0} \cdot \lambda \mathrm{e}^{-\lambda t}$$

where $\lambda > 0$.

Here are some examples of exponential pdfs:



4.2 The Cumulative Distribution Function (CDF)

The **cumulative distribution function** is defined as:

$$\begin{aligned} F(t) &\stackrel{\text{def}}{=} \Pr(T \leq t) \\ &= \int_{u=-\infty}^{t} f(u) du \end{aligned}$$

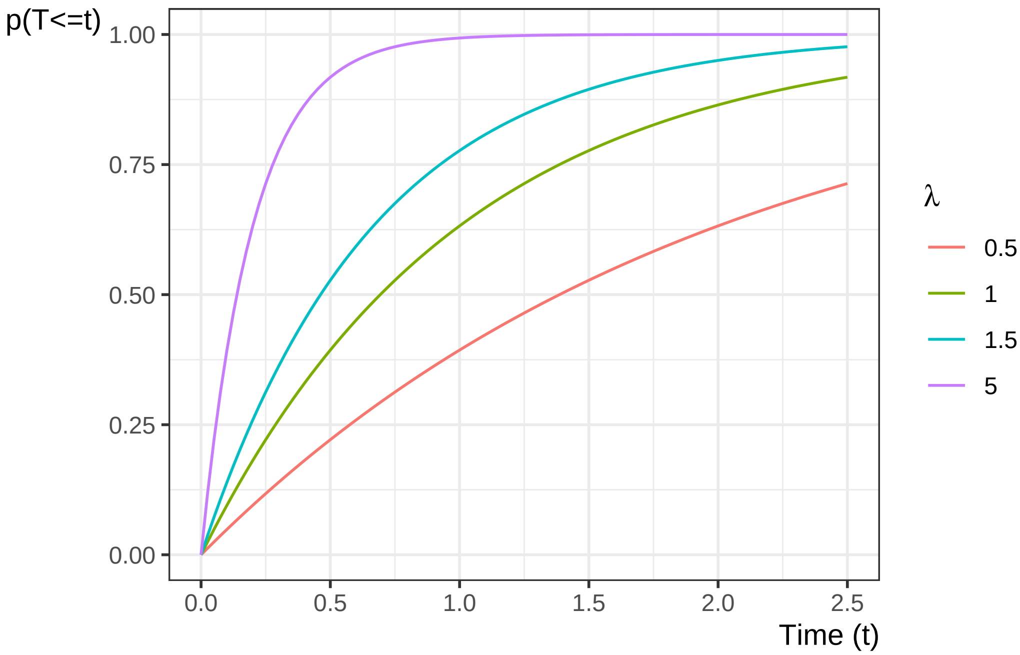
Exm

Example 4.2 (exponential distribution)**.** Recall from Epi 202: the cdf of the exponential distribution family of models is:

$$P(T \leq t) = 1_{t \geq 0} \cdot (1 - \mathrm{e}^{-\lambda t})$$

where $\lambda > 0$.

Here are some examples of exponential cdfs:



4.3 The Survival Function

For survival data, a more important quantity is the **survival function**:

Definition 4.1 (Survival function)**.**
Given a random time-to-event variable T, the **survival function** or **survivor function**, denoted $\mathrm{S}(t)$, is the probability that the event time is later than t. If the event in a clinical trial is death, then $\mathrm{S}(t)$ is the expected fraction of the original population at time 0 who have survived up to time t and are still alive at time t; that is:

$$\mathrm{S}(t) \stackrel{\text{def}}{=} \Pr(T > t)$$

Theorem 4.1 (Equivalent expressions for the survival function)**.**

$$\begin{aligned}
\mathrm{S}(t) &\stackrel{def}{=} \Pr(T > t) \\
&= \int_{u=t}^{\infty} p(u)du \\
&= 1 - F(t)
\end{aligned}$$

Exm

Example 4.3 (exponential distribution)**.** Since $\mathrm{S}(t) = 1 - F(t)$, the survival function of the exponential distribution family of models is:

$$P(T > t) = \begin{cases} \mathrm{e}^{-\lambda t}, & t \geq 0 \\ 1, & t \leq 0 \end{cases}$$

where $\lambda > 0$.
Figure 1 shows some examples of exponential survival functions.

```r
library(ggplot2)
ggplot() +
  geom_function(
    aes(col = "0.5"),
    fun = pexp,
    args = list(lower.tail = FALSE, rate = 0.5)
  ) +
  geom_function(
    aes(col = "1"),
    fun = pexp,
    args = list(lower.tail = FALSE, rate = 1)
  ) +
  geom_function(
    aes(col = "1.5"),
    fun = pexp,
    args = list(lower.tail = FALSE, rate = 1.5)
  ) +
  geom_function(
    aes(col = "5"),
    fun = pexp,
    args = list(lower.tail = FALSE, rate = 5)
  ) +
  theme_bw() +
  ylab("S(t)") +
  guides(col = guide_legend(title = expr(lambda))) +
  xlab("Time (t)") +
  xlim(0, 2.5) +
  theme(
    legend.position = "bottom",
    axis.title.x =
      element_text(
        angle = 0,
        vjust = 1,
        hjust = 1
      ),
    axis.title.y =
      element_text(
        angle = 0,
        vjust = 1,
        hjust = 1
      )
  )
```

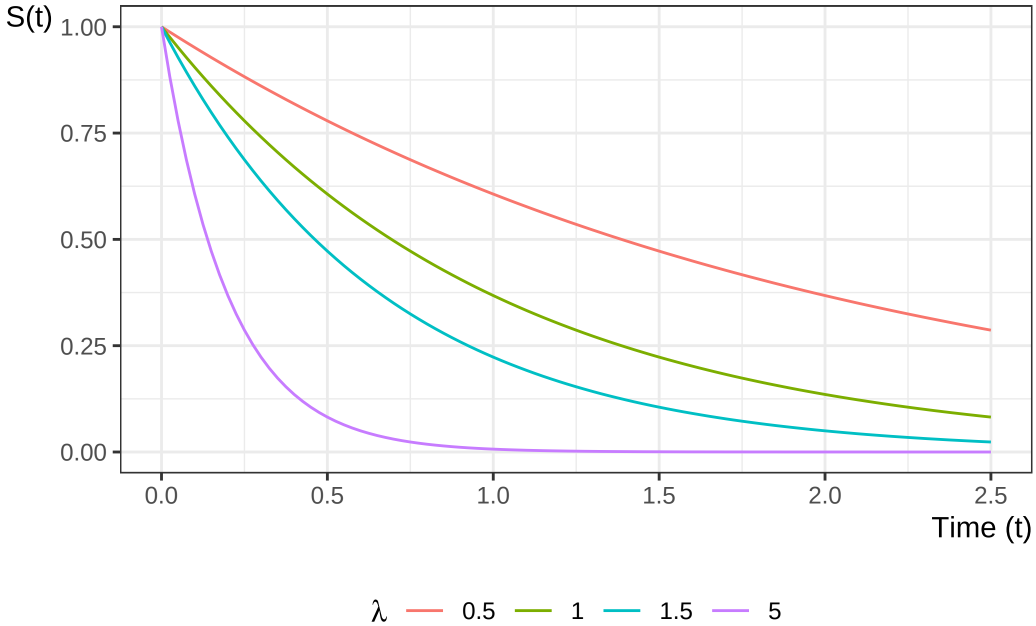


Figure 1: Exponential Survival Functions

Theorem 4.2 (Survival function as expected survival status)**.** *If A_t represents survival status at time t, with $A_t = 1$ denoting alive at time t and $A_t = 0$ denoting deceased at time t, then:*

$$\mathrm{S}(t) = \mathrm{P}(A_t = 1) = \mathrm{E}[A_t]$$

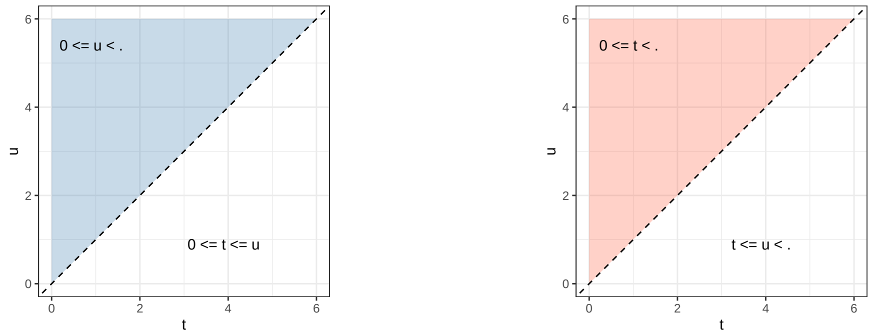
Theorem 4.3 (Mean as the integral of the survival function)**.** *If T is a nonnegative random variable, then:*

$$\mathrm{E}[T] = \int_{t=0}^{\infty} \mathrm{S}(t)\, dt$$

Proof

Proof. Adapted from the StatProofBook proof "Mean of non-negative random variable" (Soch 2023) at https://statproofbook.github.io/P/mean-nnrvar.html.

```r
library(ggplot2)
u_max <- 6
tri_df <- data.frame(t = c(0, u_max, 0), u = c(0, u_max, u_max))
ggplot(tri_df, aes(x = t, y = u)) +
  geom_polygon(fill = "steelblue", alpha = 0.3) +
  geom_abline(slope = 1, intercept = 0, linetype = "dashed") +
  annotate(
    "text",
    x = 0.65 * u_max,
    y = 0.15 * u_max,
    label = "0   t   u"
  ) +
  annotate(
    "text",
    x = 0.15 * u_max,
    y = 0.9 * u_max,
    label = "0   u < ∞"
  ) +
  coord_fixed() +
  theme_bw() +
  labs(x = "t", y = "u")
library(ggplot2)
u_max <- 6
tri_df <- data.frame(t = c(0, u_max, 0), u = c(0, u_max, u_max))
ggplot(tri_df, aes(x = t, y = u)) +
  geom_polygon(fill = "tomato", alpha = 0.3) +
  geom_abline(slope = 1, intercept = 0, linetype = "dashed") +
  annotate(
    "text",
    x = 0.15 * u_max,
    y = 0.9 * u_max,
    label = "0   t < ∞"
  ) +
  annotate(
    "text",
    x = 0.65 * u_max,
    y = 0.15 * u_max,
    label = "t   u < ∞"
  ) +
  coord_fixed() +
  theme_bw() +
  labs(x = "t", y = "u")
```



(a) Original order: for each u, t ranges over $[0, u]$. (b) Reversed order: for each t, u ranges over $[t, \infty)$.

Figure 2: The same triangular region in the (t, u)-plane, described in two equivalent ways: $0 \le t \le u < \infty$ (left, original order) and $0 \le t < \infty,\ t \le u < \infty$ (right, reversed order).

Figure 2 shows the same integration region under the two equivalent orderings. Since $\mathrm{f}(u) \ge 0$, the third step below swaps the order of integration by Tonelli's theorem (see the Fubini–Tonelli proof of the survival-function mean theorem[a] in the probability chapter for the formal argument):

$$\begin{aligned}
\mathrm{E}[T] &= \int_{u=0}^{\infty} u\,\mathrm{f}(u)\,du \\
&= \int_{u=0}^{\infty} \left(\int_{t=0}^{u} 1\,dt \right) \mathrm{f}(u)\,du \\
&= \int_{u=0}^{\infty} \int_{t=0}^{u} \mathrm{f}(u)\,dt\,du \\
&= \int_{t=0}^{\infty} \int_{u=t}^{\infty} \mathrm{f}(u)\,du\,dt \\
&= \int_{t=0}^{\infty} \mathrm{P}(T > t)\,dt \\
&= \int_{t=0}^{\infty} \mathrm{S}(t)\,dt.
\end{aligned}$$

□

[a] probability.qmd#thm-surv-mean

4.4 The Inverse Survival Function

Definition 4.2 (Inverse survival function)**.** Given a random time-to-event variable T with survival function $\mathrm{S}(t)$ (Definition 4.1), the **inverse survival function** (ISF), also called the **survival quantile function** (SQF), $\mathrm{S}^{-1}(p)$ is the earliest time t at which the survival probability has fallen to or below p:

$$\mathrm{S}^{-1}(p) \stackrel{\text{def}}{=} \inf\{t \ge 0 : \mathrm{S}(t) \le p\}, \quad 0 < p < 1.$$

Exm

Example 4.4 (Exponential distribution)**.** For an exponential distribution with rate $\lambda > 0$, the survival function is $\mathrm{S}(t) = \mathrm{e}^{-\lambda t}$.
Setting $\mathrm{S}(t) = p$ and solving for t:

$$
\begin{aligned}
\mathrm{e}^{-\lambda t} &= p \\
-\lambda t &= \log\{p\} \\
t &= \frac{-\log\{p\}}{\lambda},
\end{aligned}
$$

so the inverse survival function of the exponential distribution is:

$$
\mathrm{S}^{-1}(p) = \frac{-\log\{p\}}{\lambda}.
$$

```r
library(ggplot2)

p_seq <- seq(0.001, 0.999, length.out = 500)
rates <- c(0.5, 1, 2, 4)

df_isf <- do.call(rbind, lapply(rates, function(lam) {
  data.frame(
    p = p_seq,
    isf = -log(p_seq) / lam,
    lambda = factor(
      paste0("  = ", lam),
      levels = paste0("  = ", rates)
    )
  )
}))

ggplot(df_isf, aes(x = p, y = isf, color = lambda)) +
  geom_line() +
  labs(
    x = expression(p),
    y = expression(S^{-1}*(p)),
    color = NULL
  ) +
  theme_bw()
```

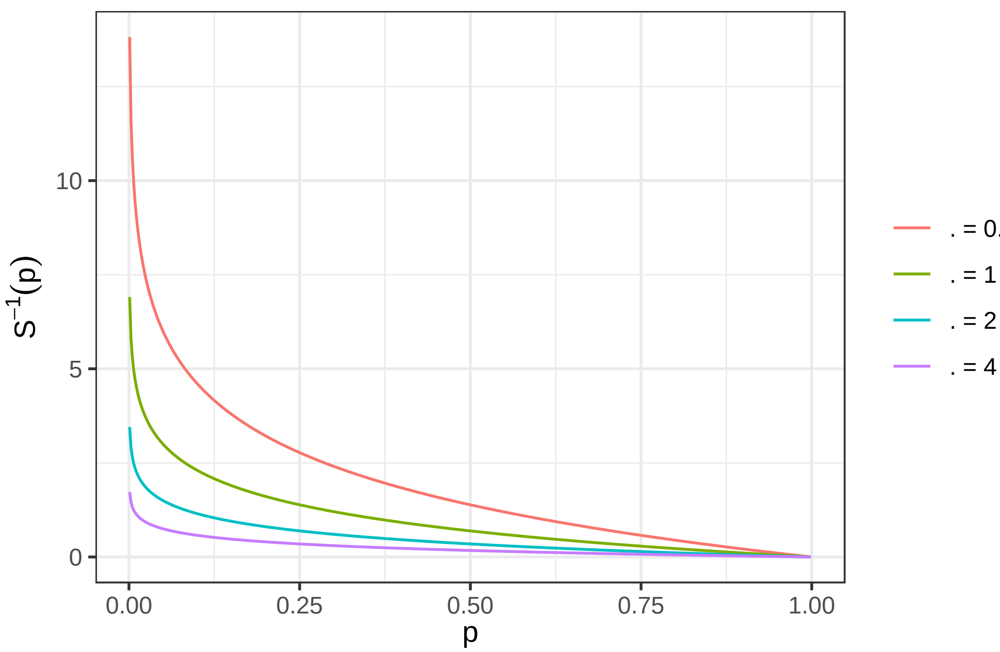


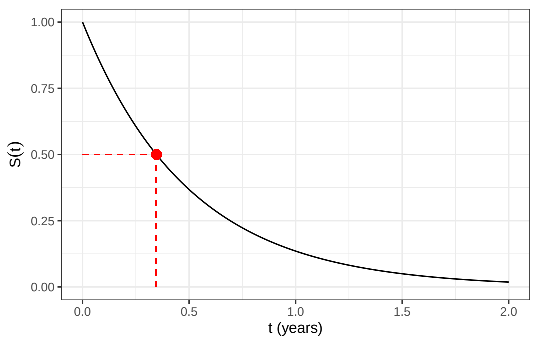
Figure 3: Exponential inverse survival function $\mathrm{S}^{-1}(p) = -\log(p)/\lambda$ for various rate parameters λ.

Numerical example. Suppose patients in a clinical trial have exponentially distributed survival times with rate $\lambda = 2$ events per year. What is the median survival time?
The median survival time is the time t at which half the patients are still alive, i.e. $\mathrm{S}(t) = 0.5$:

$$\mathrm{S}^{-1}(0.5) = \frac{-\log\{0.5\}}{2} = \frac{\log\{2\}}{2} \approx \frac{0.693}{2} \approx 0.347 \text{ years.}$$

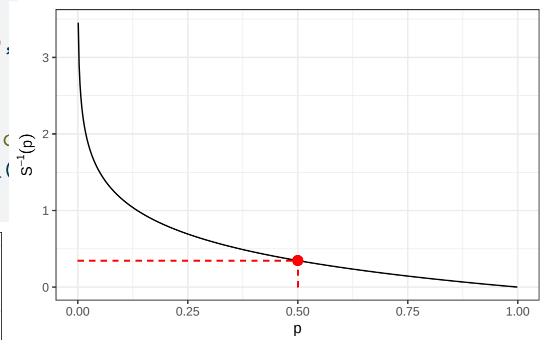
Figure 4a and Figure 4b show the survival function $\mathrm{S}(t) = \mathrm{e}^{-2t}$ and the inverse survival function $\mathrm{S}^{-1}(p) = -\log(p)/2$, each with the median survival point highlighted.

```r
library(ggplot2)

lam <- 2
t_med <- log(2) / lam
t_seq <- seq(0, 2, length.out = 500)
p_seq <- seq(0.001, 0.999, length.out

ggplot(
  data.frame(t = t_seq, s = exp(-lam *
  aes(x = t, y = s)
) +
  geom_line() +
  geom_segment(
    aes(x = 0, xend = t_med, y = 0.5,
    linetype = "dashed", color = "red"
  ) +
  geom_segment(
    aes(x = t_med, xend = t_med, y = 0,
    linetype = "dashed", color = "red"
  ) +
  geom_point(aes(x = t_med, y = 0.5), c
  labs(x = "t (years)", y = expression(
  theme_bw()
```



(a) Survival function $\mathrm{S}(t)$.

```r
ggplot(
  data.frame(p = p_seq, isf = -log(p_seq) / lam),
  aes(x = p, y = isf)
) +
  geom_line() +
  geom_segment(
    aes(x = 0.5, xend = 0.5, y = 0, yend = t_med),
    linetype = "dashed", color = "red"
  ) +
  geom_segment(
    aes(x = 0, xend = 0.5, y = t_med, yend = t_med),
    linetype = "dashed", color = "red"
  ) +
  geom_point(aes(x = 0.5, y = t_med), color = "red", size =
  labs(x = "p", y = expression(S^{-1}*(p))) +
  theme_bw()
```



(b) Inverse survival function $\mathrm{S}^{-1}(p)$.

Figure 4: For $\lambda = 2$, the survival function $\mathrm{S}(t)$ (Figure 4a) and inverse survival function $\mathrm{S}^{-1}(p)$ (Figure 4b), with the median survival time $\mathrm{S}^{-1}(0.5) \approx 0.347$ years shown as a red point.

In R:

```r
qexp(p = 0.5, rate = 2)
#> [1] 0.346574
```

Theorem 4.4 (Inverse survival function is the quantile function). *The inverse survival function equals the $(1-p)$th population quantile*[a] *of T:*

$$\mathrm{S}^{-1}(p) = Q(1-p),$$

where $Q(u) = \inf\{t : \mathrm{F}(t) \geq u\}$ is the quantile function of T.

[a] probability.qmd#def-quantile-function

Proof

Proof. Since $\mathrm{S}(t) = 1 - \mathrm{F}(t)$,

$$\begin{aligned}\mathrm{S}(t) \leq p &\iff 1 - \mathrm{F}(t) \leq p \\ &\iff \mathrm{F}(t) \geq 1 - p.\end{aligned}$$

Therefore,

$$\mathrm{S}^{-1}(p) = \inf\{t \geq 0 : \mathrm{S}(t) \leq p\} = \inf\{t \geq 0 : \mathrm{F}(t) \geq 1 - p\}.$$

Since $T \geq 0$ almost surely, $\mathrm{F}(t) = 0 < 1 - p$ for all $t < 0$ (using $p < 1$), so no $t < 0$ satisfies $\mathrm{F}(t) \geq 1 - p$; hence the constraint $t \geq 0$ is redundant and can be dropped:

$$\inf\{t \geq 0 : \mathrm{F}(t) \geq 1 - p\} = \inf\{t : \mathrm{F}(t) \geq 1 - p\} = Q(1 - p).$$

□

4.5 The Hazard Function

Another important quantity is the **hazard function**:

Definition 4.3 (Hazard function, hazard rate, hazard rate function)**.**
The **hazard function**, **hazard rate**, **hazard rate function**, for a random variable T at value t, typically denoted as $\mathrm{h}(t)$ [2] or $\lambda(t)$, [3] is the conditional density[a] of T at t, given $T \geq t$. That is:

$$\lambda(t) \stackrel{\text{def}}{=} \mathrm{p}(T = t | T \geq t)$$

If T represents the time at which an event occurs, then $\lambda(t)$ is the probability that the event occurs at time t, given that it has not occurred prior to time t.
The name "hazard" carries a connotation that the event is undesirable — death, relapse, equipment failure, etc. When the event in question is neutral or desirable (recovery, conception, graduation, response to treatment), the same quantity $\lambda(t)$ is often called the **event incidence rate** instead. This is parallel to the convention that conditional probabilities of undesirable events are called **risks**, while the same conditional probabilities for neutral/desirable events are simply called **probabilities**. The math is identical; only the name changes with the valence of the event.

[a] probability.qmd#def-pdf

Definition 4.4 (Incidence rate)**.** Given a population of N individuals indexed by i, each with their own hazard rate $\lambda_i(t)$, the **incidence rate** for that population is the mean hazard rate:

$$\bar{\lambda}(t) \stackrel{\text{def}}{=} \frac{1}{N} \sum_{i=1}^{N} \lambda_i(t)$$

Theorem 4.5 (Incidence rate in a homogenous population)**.** *If a population of individuals indexed by i all have identical hazard rates $\lambda_i(t) = \lambda(t)$, then the* ***incidence rate*** *for that population is equal to the hazard rate:*

[3] for example in Dobson and Barnett (2018), Vittinghoff et al. (2012), Klein and Moeschberger (2003), and Kleinbaum and Klein (2012)

[3] for example, in Rothman et al. (2021) and Kalbfleisch and Prentice (2011)

$$\bar{\lambda}(t) = \lambda(t)$$

The hazard function has an important relationship to the density and survival functions, which we can use to derive the hazard function for a given probability distribution (Theorem 4.6).

Lemma 4.1 (Joint probability of a variable with itself)**.**

$$p(T = t, T \geq t) = p(T = t)$$

Proof

Proof. By the subset property[a], if $A \subseteq B$ then $\Pr(A \cap B) = \Pr(A)$. In particular, $\{T = t\} \subseteq \{T \geq t\}$, so $p(T = t, T \geq t) = p(T = t)$. □

[a] probability.qmd#thm-prob-subset

Theorem 4.6 (Hazard equals density over survival)**.**

$$\lambda(t) = \frac{f(t)}{\mathrm{S}(t)}$$

Proof

Proof.

$$\begin{aligned}
\lambda(t) &= p(T = t | T \geq t) \\
&= \frac{p(T = t, T \geq t)}{p(T \geq t)} \\
&= \frac{p(T = t)}{p(T \geq t)} \\
&= \frac{f(t)}{\mathrm{S}(t)}
\end{aligned}$$

□

Exm

Example 4.5 (exponential distribution)**.** The hazard function of the exponential distribution family of models is:

$$\begin{aligned}
P(T = t | T \geq t) &= \frac{f(t)}{\mathrm{S}(t)} \\
&= \frac{1_{t \geq 0} \cdot \lambda \mathrm{e}^{-\lambda t}}{\mathrm{e}^{-\lambda t}} \\
&= 1_{t \geq 0} \cdot \lambda
\end{aligned}$$

Figure 5 shows some examples of exponential hazard functions.

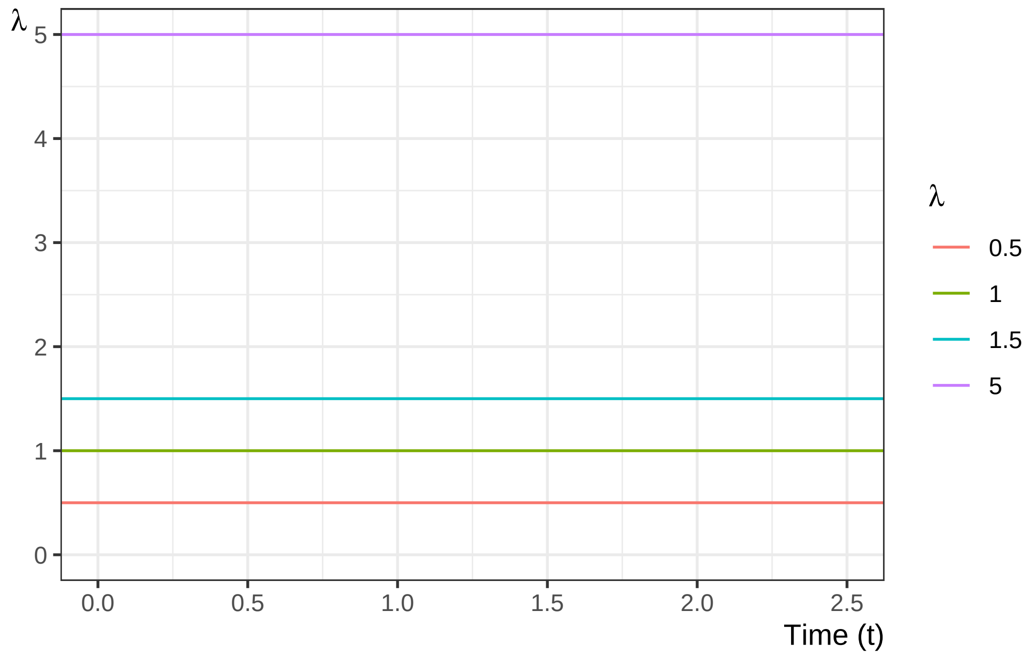


Figure 5: Examples of hazard functions for exponential distributions

---

We can also view the hazard function as the derivative of the negative of the logarithm of the survival function:

Theorem 4.7 (transform survival to hazard)**.**

$$\lambda(t) = \frac{\partial}{\partial t}\{-\log \mathrm{S}(t)\}$$

Proof

Proof.

$$\begin{aligned}\lambda(t) &= \frac{f(t)}{\mathrm{S}(t)} \\ &= \frac{-S'(t)}{\mathrm{S}(t)} \\ &= -\frac{S'(t)}{\mathrm{S}(t)} \\ &= -\frac{\partial}{\partial t}\log \mathrm{S}(t) \\ &= \frac{\partial}{\partial t}\{-\log \mathrm{S}(t)\}\end{aligned}$$

□

Definition 4.5 (hazard ratio)**.**

$$\theta_{\lambda}(t|\tilde{x}:\tilde{x}^*) \stackrel{\text{def}}{=} \frac{\lambda(t|\tilde{x})}{\lambda(t|\tilde{x}^*)}$$

Definition 4.6 (Conditional survival probability at an event time)**.** At event time t_i, the **conditional survival probability** is

$$\kappa_i \stackrel{\text{def}}{=} \mathrm{p}(T > t_i \mid T \geq t_i).$$

Theorem 4.8 (Conditional survival is the complement of the discrete hazard increment)**.** *Let $\lambda_i \stackrel{def}{=} \mathrm{p}(T = t_i \mid T \geq t_i)$ be the discrete hazard increment at event time t_i. Then $\kappa_i = 1 - \lambda_i$.*

Proof

Proof.

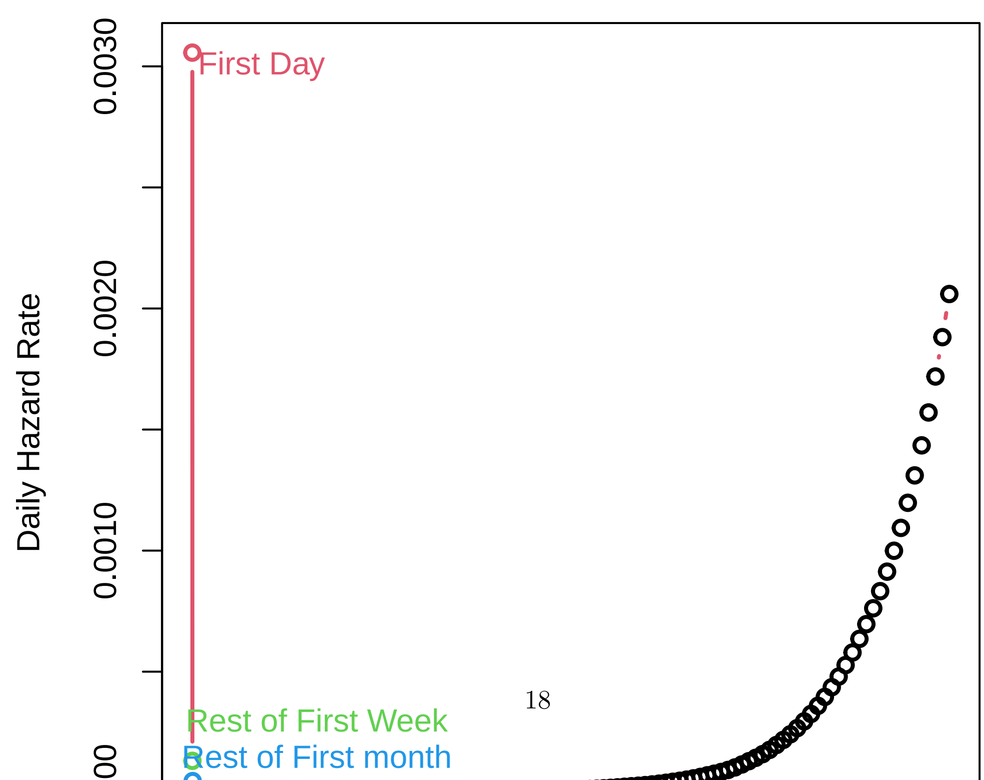
$$\begin{aligned} \kappa_i &= \mathrm{p}(T > t_i \mid T \geq t_i) \\ &= 1 - \mathrm{p}(T \leq t_i \mid T \geq t_i) \\ &= 1 - \mathrm{p}(T = t_i \mid T \geq t_i) \\ &= 1 - \lambda_i. \end{aligned}$$

□

Exm

Example 4.6 (Time to death in the US in 2004)**.** The first day is the most dangerous:

```r
# survexp.rda is stored locally in Data/survexp.rda
# newer versions of survival dropped the first-year age breakdown

fs::path(
  here::here(),
  "Data",
  "survexp.rda"
) |>
  load() |>
  invisible()
s1 <- survexp.us[, "female", "2004"]
age1 <- c(
  0.5 / 365.25,
  4 / 365.25,
  17.5 / 365.25,
  196.6 / 365.25,
  1:109 + 0.5
)
cols <- rep(1, 113)
cols[1] <- 2
cols[2] <- 3
cols[3] <- 4

plot(
  age1, s1,
  type = "b", lwd = 2,
  xlab = "Age", ylab = "Daily Hazard Rate",
  col = cols
)

text(10, .003, "First Day", col = 2)
text(18, .00030, "Rest of First Week", col = 3)
text(18, .00015, "Rest of First month", col = 4)
```



```r
yrs <- 1:40
s1 <- survexp.us[5:113, "male", "2004"]
s2 <- survexp.us[5:113, "female", "2004"]

age1 <- 1:109

plot(
  age1[yrs], s1[yrs],
  type = "l", lwd = 2,
  xlab = "Age", ylab = "Daily Hazard Rate"
)
lines(age1[yrs], s2[yrs], col = 2, lwd = 2)
legend(5, 5e-6, c("Males", "Females"), col = 1:2, lwd = 2)
```

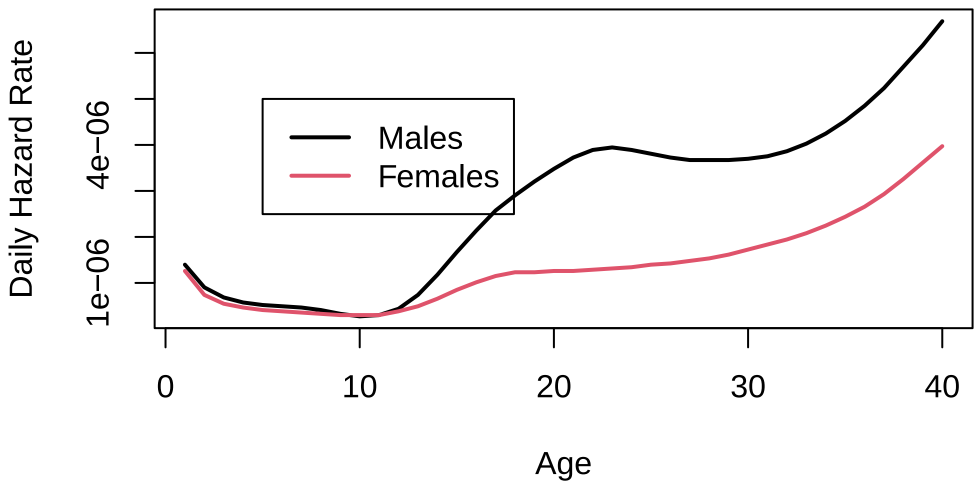


Figure 7: Daily Hazard Rates in 2004 for US Males and Females 1-40

```r
s1 <- survexp.us[, "female", "2004"]

s2 <- 365.25 * s1[5:113]
s2 <- c(s1[1], 6 * s1[2], 21 * s1[3], 337.25 * s1[4], s2)
cs2 <- cumsum(s2)
age2 <- c(1 / 365.25, 7 / 365.25, 28 / 365.25, 1:110)
plot(age2, exp(-cs2), type = "l", lwd = 2, xlab = "Age", ylab = "Survival")
```

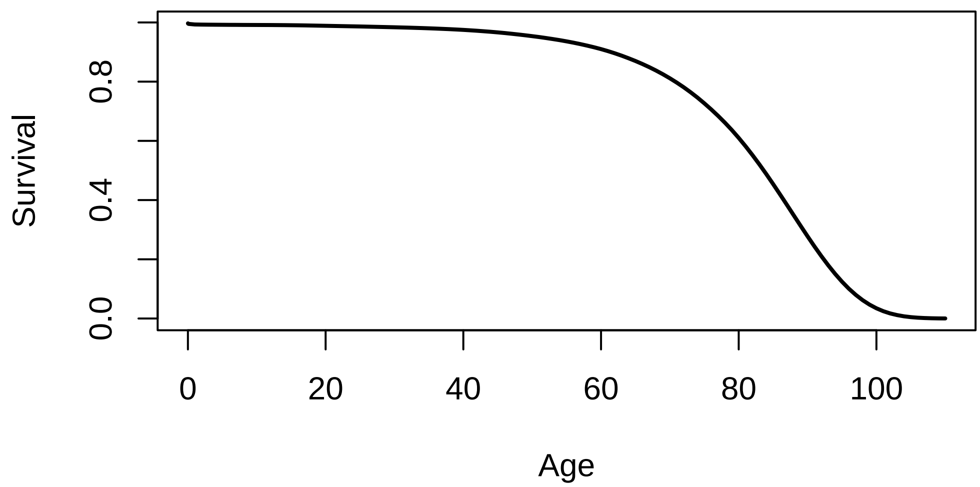


Figure 8: Survival Curve in 2004 for US Females

Exercise 4.1. Why do the male and female hazard functions in Figure 7 differ where they do?

Exercise 4.2. Compare and contrast Figure 8 with Figure 6.

4.6 The Cumulative Hazard Function

Since $\lambda(t) = \frac{\partial}{\partial t}\{-\log \mathrm{S}(t)\}$ (see Theorem 4.7), we also have:

Corollary 4.1 (Survival function from the cumulative hazard)**.**

$$\mathrm{S}(t) = \exp\left\{-\int_{u=0}^{t} \lambda(u)du\right\} \tag{1}$$

The integral in Equation 1 is important enough to have its own name: **cumulative hazard**.

Definition 4.7 (cumulative hazard)**.** The **cumulative hazard function**, often denoted $\Lambda(t)$ or $\mathrm{H}(t)$, is defined as:

$$\Lambda(t) \stackrel{\text{def}}{=} \int_{u=0}^{t} \lambda(u)du$$

As we will see below, $\Lambda(t)$ is tractable to estimate, and we can then derive an estimate of the hazard function using an approximate derivative of the estimated cumulative hazard.

Exm

Example 4.7. The cumulative hazard function for the exponential distribution with rate parameter λ is:

$$\Lambda(t) = \mathbb{1}_{t \geq 0} \cdot \lambda t$$

Figure 9 shows some examples of exponential cumulative hazard functions.

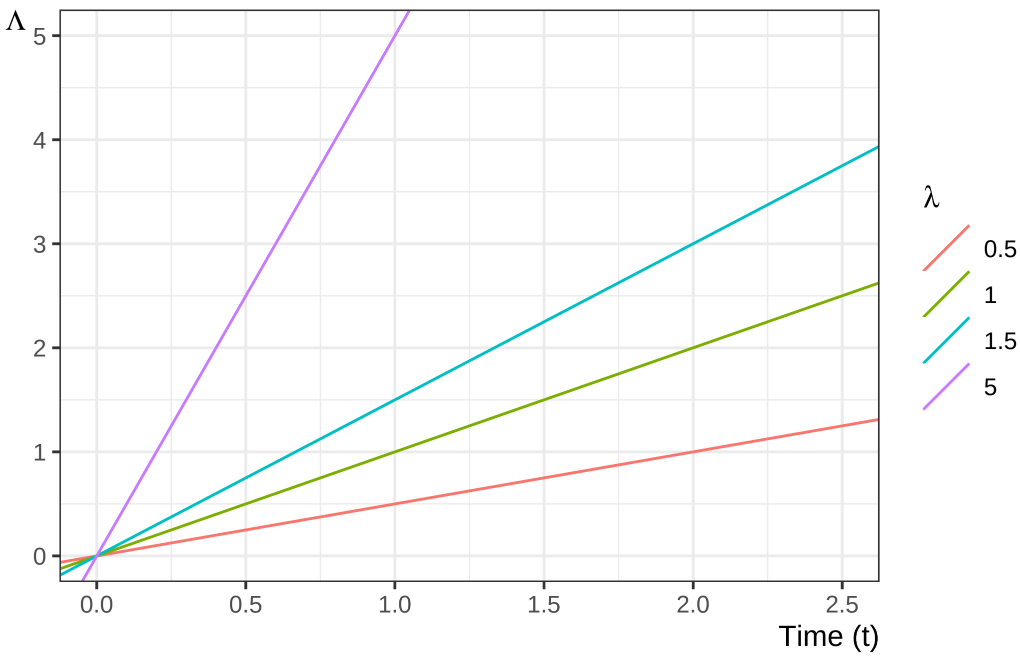


Figure 9: Examples of exponential cumulative hazard functions

4.7 Some Key Mathematical Relationships among Survival Concepts

Diagram:

$$\mathrm{f}(t) \xleftarrow[\mathrm{S}(t)\lambda(t)]{-S'(t)} \mathrm{S}(t) \xleftarrow{\exp\{-\Lambda(t)\}} \Lambda(t) \xleftarrow{\int_{u=0}^{t} \lambda(u)du} \lambda(t) \xleftarrow{\exp\{\eta(t)\}} \eta(t)$$

$$\mathrm{f}(t) \xrightarrow[\int_{u=t}^{\infty} \mathrm{f}(u)du]{\mathrm{f}(t)/\lambda(t)} \mathrm{S}(t) \xrightarrow[-\log \mathrm{S}(t)]{} \Lambda(t) \xrightarrow[\Lambda'(t)]{} \lambda(t) \xrightarrow[\log\{\lambda(t)\}]{} \eta(t)$$

Identities:

$$
\begin{aligned}
\mathrm{S}(t) &= 1 - \mathrm{F}(t) \\
&= \exp\{-\Lambda(t)\} \\
\mathrm{S}'(t) &= -f(t) \\
\Lambda(t) &= -\log\{\mathrm{S}(t)\} \\
\Lambda'(t) &= \lambda(t) \\
\lambda(t) &= \frac{\mathrm{f}(t)}{\mathrm{S}(t)} \\
&= -\frac{\partial}{\partial t} \log \mathrm{S}(t) \\
f(t) &= \lambda(t) \cdot \mathrm{S}(t)
\end{aligned}
$$

Some proofs (others left as exercises):

$$
\begin{aligned}
\mathrm{S}'(t) &= \frac{\partial}{\partial t}(1 - \mathrm{F}(t)) \\
&= -\mathrm{F}'(t) \\
&= -\mathrm{f}(t)
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial}{\partial t} \log\{\mathrm{S}(t)\} &= \frac{\mathrm{S}'(t)}{\mathrm{S}(t)} \\
&= -\frac{\mathrm{f}(t)}{\mathrm{S}(t)} \\
&= -\lambda(t)
\end{aligned}
$$

$$
\begin{aligned}
\Lambda(t) &\stackrel{\text{def}}{=} \int_{u=0}^{t} \lambda(u) du \\
&= \int_0^t -\frac{\partial}{\partial u} \log\{\mathrm{S}(u)\} du \\
&= [-\log\{\mathrm{S}(u)\}]_{u=0}^{u=t} \\
&= [\log\{\mathrm{S}(u)\}]_{u=t}^{u=0} \\
&= \log\{\mathrm{S}(0)\} - \log\{\mathrm{S}(t)\} \\
&= \log\{1\} - \log\{\mathrm{S}(t)\} \\
&= 0 - \log\{\mathrm{S}(t)\} \\
&= -\log\{\mathrm{S}(t)\}
\end{aligned}
$$

Corollary:

$$
\mathrm{S}(t) = \exp\{-\Lambda(t)\}
$$

4.8 Likelihood with censoring

If an event time T is observed exactly as $T = t$, then the likelihood of that observation is just its probability density function:

$$
\begin{aligned}
\mathcal{L}(t) &= \mathrm{f}(T = t) \\
&\stackrel{\text{def}}{=} \mathrm{f}_T(t) \\
&= \lambda_T(t)\,\mathrm{S}_T(t) \\
\ell(t) &\stackrel{\text{def}}{=} \log\{\mathcal{L}(t)\} \\
&= \log\{\lambda_T(t)\,\mathrm{S}_T(t)\} \\
&= \log\{\lambda_T(t)\} + \log\{\mathrm{S}_T(t)\} \\
&= \log\{\lambda_T(t)\} - \Lambda_T(t)
\end{aligned}
$$

If instead the event time T is censored and only known to be after time y, then the likelihood of that censored observation is instead the survival function evaluated at the censoring time:

$$
\begin{aligned}
\mathcal{L}(y) &= p_T(T > y) \\
&\stackrel{\text{def}}{=} \mathrm{S}_T(y) \\
\ell(y) &\stackrel{\text{def}}{=} \log\{\mathcal{L}(y)\} \\
&= \log\{\mathrm{S}(y)\} \\
&= -\Lambda(y)
\end{aligned}
$$

What's written above is incomplete. We also observed whether or not the observation was censored. Let C denote the time when censoring would occur (if the event did not occur first); let $f_C(y)$ and $S_C(y)$ be the corresponding density and survival functions for the censoring event.

Let Y denote the time when observation ended (either by censoring or by the event of interest occurring), and let D be an indicator variable for the event occurring at Y (so $D = 0$ represents a censored observation and $D = 1$ represents an uncensored observation). In other words, let $Y \stackrel{\text{def}}{=} \min(T, C)$ and $D \stackrel{\text{def}}{=} \mathbb{1}\{T <= C\}$.

Then the complete likelihood of the observed data (Y, D) is:

$$
\begin{aligned}
\mathcal{L}(y, d) &= \mathrm{p}(Y = y, D = d) \\
&= [\mathrm{p}(T = y, C > y)]^d \cdot [\mathrm{p}(T > y, C = y)]^{1-d}
\end{aligned}
$$

Typically, survival analyses assume that C and T are mutually independent; this assumption is called "non-informative" censoring.

Then the joint likelihood $\mathrm{p}(Y, D)$ factors into the product $\mathrm{p}(Y), \mathrm{p}(D)$, and the likelihood reduces to:

$$
\begin{aligned}
\mathcal{L}(y, d) &= [\mathrm{p}(T = y, C > y)]^d \cdot [\mathrm{p}(T > y, C = y)]^{1-d} \\
&= [\mathrm{p}(T = y)\,\mathrm{p}(C > y)]^d \cdot [\mathrm{p}(T > y)\,\mathrm{p}(C = y)]^{1-d} \\
&= [\mathrm{f}_T(y)\,\mathrm{S}_C(y)]^d \cdot [\mathrm{S}(y)\,\mathrm{f}_C(y)]^{1-d} \\
&= [\mathrm{f}_T(y)^d\,\mathrm{S}_C(y)^d] \cdot [\mathrm{S}_T(y)^{1-d}\,\mathrm{f}_C(y)^{1-d}] \\
&= (\mathrm{f}_T(y)^d \cdot \mathrm{S}_T(y)^{1-d}) \cdot (\mathrm{f}_C(y)^{1-d} \cdot \mathrm{S}_C(y)^d)
\end{aligned}
$$

The corresponding log-likelihood is:

$$
\begin{aligned}
\ell(y, d) &= \log\{\mathcal{L}(y, d)\} \\
&= \log\{(f_T(y)^d \cdot S_T(y)^{1-d}) \cdot (f_C(y)^{1-d} \cdot S_C(y)^d)\} \\
&= \log\{f_T(y)^d \cdot S_T(y)^{1-d}\} + \log\{f_C(y)^{1-d} \cdot S_C(y)^d\}
\end{aligned}
$$

Let

- θ_T represent the parameters of $p_T(t)$,
- θ_C represent the parameters of $p_C(c)$,
- $\theta = (\theta_T, \theta_C)$ be the combined vector of all parameters.

The corresponding score function is:

$$
\begin{aligned}
\ell'(y,d) &= \frac{\partial}{\partial \theta}[\log\{f_T(y)^d \cdot S_T(y)^{1-d}\} + \log\{f_C(y)^{1-d} \cdot S_C(y)^d\}] \\
&= \left(\frac{\partial}{\partial \theta}\log\{f_T(y)^d \cdot S_T(y)^{1-d}\}\right) + \left(\frac{\partial}{\partial \theta}\log\{f_C(y)^{1-d} \cdot S_C(y)^d\}\right)
\end{aligned}
$$

As long as θ_C and θ_T don't share any parameters, then if censoring is non-informative, the partial derivative with respect to θ_T is:

$$
\begin{aligned}
\ell'_{\theta_T}(y,d) &\stackrel{\text{def}}{=} \frac{\partial}{\partial \theta_T}\ell(y,d) \\
&= \left(\frac{\partial}{\partial \theta_T}\log\left\{f_T(y)^d \cdot S_T(y)^{1-d}\right\}\right) + \left(\frac{\partial}{\partial \theta_T}\log\left\{f_C(y)^{1-d} \cdot S_C(y)^d\right\}\right) \\
&= \left(\frac{\partial}{\partial \theta_T}\log\left\{f_T(y)^d \cdot S_T(y)^{1-d}\right\}\right) + 0 \\
&= \frac{\partial}{\partial \theta_T}\log\left\{f_T(y)^d \cdot S_T(y)^{1-d}\right\}
\end{aligned}
$$

Thus, the MLE for θ_T won't depend on θ_C, and we can ignore the distribution of C when estimating the parameters of $f_T(t) = p(T = t)$.

Then:

$$
\begin{aligned}
\mathcal{L}(y,d) &= f_T(y)^d \cdot S_T(y)^{1-d} \\
&= (h_T(y)^d S_T(y)^d) \cdot S_T(y)^{1-d} \\
&= h_T(y)^d \cdot S_T(y)^d \cdot S_T(y)^{1-d} \\
&= h_T(y)^d \cdot S_T(y) \\
&= S_T(y) \cdot h_T(y)^d
\end{aligned}
$$

That is, if the event occurred at time y (i.e., if $d = 1$), then the likelihood of $(Y, D) = (y, d)$ is equal to the hazard function at y times the survival function at y. Otherwise, the likelihood is equal to just the survival function at y.

The corresponding log-likelihood is:

$$
\begin{aligned}
\ell(y,d) &= \log\left\{\mathcal{L}(y,d)\right\} \\
&= \log\left\{S_T(y) \cdot h_T(y)^d\right\} \\
&= \log\left\{S_T(y)\right\} + \log\left\{h_T(y)^d\right\} \\
&= \log\left\{S_T(y)\right\} + d \cdot \log\left\{h_T(y)\right\} \\
&= -H_T(y) + d \cdot \log\left\{h_T(y)\right\}
\end{aligned}
$$

In other words, the log-likelihood contribution from a single observation $(Y, D) = (y, d)$ is equal to the negative cumulative hazard at y, plus the log of the hazard at y if the event occurred at time y.

5 Parametric Models for Time-to-Event Outcomes

5.1 Exponential Distribution

- The exponential distribution is the base distribution for survival analysis.
- The distribution has a constant hazard λ
- The mean survival time is λ^{-1}

Mathematical details of exponential distribution

$$
\begin{aligned}
f(t) &= \lambda \mathrm{e}^{-\lambda t} \\
F(t) &= 1 - \mathrm{e}^{-\lambda t} \\
\mathrm{S}(t) &= \mathrm{e}^{-\lambda t} \\
\log\{\mathrm{S}(t)\} &= -\lambda t \\
\lambda(t) &= \frac{f(t)}{\mathrm{S}(t)} = \frac{\lambda \mathrm{e}^{-\lambda t}}{\mathrm{e}^{-\lambda t}} = \lambda \\
E(t) &= \lambda^{-1} \\
Var(t) &= \lambda^{-2} \\
\log\{f(t)\} &= \log\{\lambda\} - \lambda t \\
\frac{\partial}{\partial \lambda} \log\{f(t)\} &= \lambda^{-1} - t \\
&= \mathrm{E}[t] - t \\
&= -(\mathrm{E}[t] - t) \\
&= -\varepsilon
\end{aligned}
$$

Prediction intervals for time-to-event outcomes

Exercise 5.1 (Construct a prediction interval)**.** Suppose a cancer patient is predicted to have an expected (mean) lifetime of 7 years after diagnosis, and suppose the distribution is exponential.
Construct a 95% prediction interval for survival.

Tip

Use the quantiles of the exponential distribution.

Solution

Solution 5.1. If the mean is 7 years until death, then the rate parameter $\lambda = 1/7$ events (deaths) per year.
The 0.025 quantile of the exponential distribution with $\lambda = 1/7$ is `qexp(p 0.025, rate = 1/7)` $= 0.177225$ and the 0.975 quantile is `qexp(p 0.975, rate = 1/7)` $= 25.822156$, so the prediction interval is `qexp(p c(.025, 0.975), rate = 1/7)` $= (0.177225, 25.822156)$.

Exercise 5.2. Graph the prediction interval as a function of the mean, for Gaussian ($\sigma = 1$), Binomial, Poisson, and Exponential.

Solution

Solution 5.2. Left to the reader for now.

Exercise 5.3 (Explain the results)**.** Why do time-to-event models have such wide predictive intervals?

Tip

Consider the relationship between the mean, variance, and standard deviation of the exponential distribution, and contrast that relationship with the Poisson distribution and the Bernoulli distribution.

Solution

Solution 5.3. In the exponential distribution, variance is the square of the mean (hence SD is equal to mean); as opposed to Poisson, where variance was equal to the mean (and SD is the square-root of the mean), or the Bernoulli, where the variance is the mean minus the square of the mean (so the SD is smaller than the square-root of the mean).

Estimating λ

- Suppose we have m exponential survival times of $t_1, t_2, \dots, t_m$ and k right-censored values at $u_1, u_2, \dots, u_k$.
- A survival time of $t_i = 10$ means that subject i died at time 10. A right-censored time $u_i = 10$ means that at time 10, subject i was still alive and that we have no further follow-up.
- For the moment we will assume that the survival distribution is exponential and that all the subjects have the same parameter λ.

We have m exponential survival times of $t_1, t_2, \dots, t_m$ and k right-censored values at $u_1, u_2, \dots, u_k$. The log-likelihood of an observed survival time t_i is

$$\log\{\lambda e^{-\lambda t_i}\} = \log\{\lambda\} - \lambda t_i$$

and the likelihood of a censored value is the probability of that outcome (survival greater than u_j) so the log-likelihood is

$$\begin{aligned}\ell_j(\lambda) &= \log\{e^{-\lambda u_j}\} \\ &= -\lambda u_j\end{aligned}$$

Theorem 5.1 (MLE of the exponential rate parameter)**.** *Let $T = \sum t_i$ and $U = \sum u_j$. Then:*

$$\hat{\lambda}_{ML} = \frac{m}{T + U} \tag{2}$$

Proof

Proof.

$$\begin{aligned}
\ell(\lambda) &= \sum_{i=1}^{m}(\log\{\lambda\} - \lambda t_i) + \sum_{j=1}^{k}(-\lambda u_j) \\
&= m\log\{\lambda\} - (T+U)\lambda \\
\ell'(\lambda) &= m\lambda^{-1} - (T+U) \\
\hat{\lambda} &= \frac{m}{T+U}
\end{aligned}$$

□

$$\begin{aligned}
\ell'' &= -m/\lambda^2 \\
&< 0 \\
\hat{E}[T] &= \hat{\lambda}^{-1} \\
&= \frac{T+U}{m}
\end{aligned}$$

Fisher Information and Standard Error

$$\begin{aligned}
\mathrm{E}[-\ell''] &= m/\lambda^2 \\
\mathrm{Var}\left(\hat{\lambda}\right) &\approx (\mathrm{E}[-\ell''])^{-1} \\
&= \lambda^2/m \\
\mathrm{SE}\left(\hat{\lambda}\right) &= \sqrt{\mathrm{Var}\left(\hat{\lambda}\right)} \\
&\approx \lambda/\sqrt{m}
\end{aligned}$$

$\hat{\lambda}$ depends on the censoring times of the censored observations, but $\mathrm{Var}\left(\hat{\lambda}\right)$ only depends on the number of uncensored observations, m, and not on the number of censored observations (k).

5.2 Other Parametric Survival Distributions

- Any density on $[0, \infty)$ can be a survival distribution, but the most useful ones are all skew right.
- The most frequently used generalization of the exponential is the Weibull[4].
- Other common choices are the gamma, log-normal, log-logistic, Gompertz, inverse Gaussian, and Pareto.
- Most of what we do going forward is non-parametric or semi-parametric, but sometimes these parametric distributions provide a useful approach.

6 Nonparametric Survival Analysis

6.1 Basic ideas

- Mostly, we work without a parametric model.

[4] probability.qmd#sec-weibull

- The first task is to estimate a survival function from data listing survival times, and censoring times for censored data.
- For example one patient may have relapsed at 10 months. Another might have been followed for 32 months without a relapse having occurred (censored).
- The minimum information we need for each patient is a time and a censoring variable which is 1 if the event occurred at the indicated time and 0 if this is a censoring time.

Exm

Example 6.1 (Clinical Trial for Pediatric Acute Leukemia)**.**

Overview of study
This is from a clinical trial in 1963 for 6-MP treatment vs. placebo for acute leukemia in 42 children (Freireich et al. 1963).

- Pairs of children:
- matched by remission status at the time of treatment (`remstat`: `1` = partial, `2` = complete)
- randomized to 6-MP (exit times in `t2`) or placebo (exit times in `t1`)
- Followed until relapse or end of study.
- All of the placebo group relapsed, but some of the 6-MP group were censored (which means they were still in remission); indicated by `relapse` variable (`0` = censored, `1` = relapse).
- 6-MP = 6-Mercaptopurine (Purinethol) is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug used currently for Acute lymphoblastic leukemia (ALL). It is classified as an antimetabolite.

Study design

- Clinical trial in 1963 for 6-MP treatment vs. placebo for Acute Leukemia in 42 children.
- Pairs of children:
- matched by remission status at the time of treatment (`remstat`)
- `remstat` = 1: partial
- `remstat` = 2: complete
- randomized to 6-MP (exit time: `t2`) or placebo (`t1`).
- Followed until relapse or end of study.
- All of the placebo group relapsed,
- Some of the 6-MP group were censored.

Table 1: `drug6mp` pediatric acute leukemia data

```
library(KMsurv)
data(drug6mp)
drug6mp <- drug6mp |> tibble::as_tibble()
drug6mp
#> # A tibble: 21 x 5
#>     pair remstat    t1    t2 relapse
#>    <int>   <int> <int> <int>   <int>
#>  1     1       1     1    10       1
#>  2     2       2    22     7       1
#>  3     3       2     3    32       0
#>  4     4       2    12    23       1
#>  5     5       2     8    22       1
#>  6     6       1    17     6       1
#>  7     7       2     2    16       1
#>  8     8       2    11    34       0
#>  9     9       2     8    32       0
#> 10    10       2    12    25       0
#> # i 11 more rows
```

Data documentation for `drug6mp`

```
# library(printr) # inserts help-file output into markdown output
library(KMsurv)
?drug6mp
```

Descriptive Statistics

Table 2: Summary statistics for `drug6mp` data

```
summary(drug6mp)
#>       pair       remstat          t1             t2          relapse
#>  Min.   : 1   Min.   :1.00   Min.   : 1.00   Min.   : 6.0   Min.   :0.000
#>  1st Qu.: 6   1st Qu.:2.00   1st Qu.: 4.00   1st Qu.: 9.0   1st Qu.:0.000
#>  Median :11   Median :2.00   Median : 8.00   Median :16.0   Median :0.000
#>  Mean   :11   Mean   :1.76   Mean   : 8.67   Mean   :17.1   Mean   :0.429
#>  3rd Qu.:16   3rd Qu.:2.00   3rd Qu.:12.00   3rd Qu.:23.0   3rd Qu.:1.000
#>  Max.   :21   Max.   :2.00   Max.   :23.00   Max.   :35.0   Max.   :1.000
```

- The average time in each group is not useful. Some of the 6-MP patients have not relapsed at the time recorded, while all of the placebo patients have relapsed.
- The median time is not really useful either because so many of the 6-MP patients have not relapsed (12/21).
- Both are biased down in the 6-MP group. Remember that lower times are worse since they indicate sooner recurrence.

Exponential model

- We *can* compute the hazard rate, assuming an exponential model: number of relapses divided by the sum of the exit times (Equation 2).

$$\hat{\lambda} = \frac{\sum_{i=1}^{n} D_i}{\sum_{i=1}^{n} Y_i}$$

- For the placebo, that is just the reciprocal of the mean time:

$$
\begin{aligned}
\hat{\lambda}_{\text{placebo}} &= \frac{\sum_{i=1}^{n} D_i}{\sum_{i=1}^{n} Y_i} \\
&= \frac{\sum_{i=1}^{n} 1}{\sum_{i=1}^{n} Y_i} \\
&= \frac{n}{\sum_{i=1}^{n} Y_i} \\
&= \frac{1}{\bar{Y}} \\
&= \frac{1}{8.666667} \\
&= 0.115385
\end{aligned}
$$

- For the 6-MP group, $\hat{\lambda} = 9/359 = 0.025$

$$
\begin{aligned}
\hat{\lambda}_{\text{6-MP}} &= \frac{\sum_{i=1}^{n} D_i}{\sum_{i=1}^{n} Y_i} \\
&= \frac{9}{359} \\
&= 0.02507
\end{aligned}
$$

- The estimated hazard in the placebo group is 4.6 times as large as in the 6-MP group (assuming the hazard is constant over time).

7 The Kaplan-Meier Product Limit Estimator

7.1 Estimating survival in datasets without censoring

In the `drug6mp` dataset, the estimated survival function for the placebo patients is easy to compute. For any time t in months, $\text{S}(t)$ is the fraction of patients with times greater than t:

7.2 Estimating survival in datasets with censoring

- For the 6-MP patients, we cannot ignore the censored data because we know that the time to relapse is greater than the censoring time.
- For any time t in months, we know that 6-MP patients with times greater than t have not relapsed, and those with relapse time less than t have relapsed, but we don't know if patients with censored time less than t have relapsed or not.
- The procedure we usually use is the Kaplan-Meier product-limit estimator of the survival function.
- The Kaplan-Meier estimator is a step function (like the empirical cdf), which changes value only at the event times, not at the censoring times.
- At each event time t_i, we compute the at-risk set, which includes all observations whose event time or censoring time is at least t_i. Its size is r_i.
- If d_i of the observations have an event time (not a censoring time) of t_i, then the group of survivors immediately following time t_i is reduced by the fraction

$$
\frac{r_i - d_i}{r_i} = 1 - \frac{d_i}{r_i}
$$

```
risk_cartoon <- tibble::tibble(
  person = paste("Person", 1:8),
  exit_time = c(2, 3, 4, 5, 6, 6, 7, 8),
  status = c(
    "Event",
    "Censored",
    "Event",
    "Censored",
    "Event",
    "Censored",
    "Event",
    "Censored"
  )
) |>
  dplyr::mutate(person_id = dplyr::row_number())

risk_counts <- tibble::tibble(time = c(0, 2, 4, 6, 8)) |>
  dplyr::mutate(
    at_risk = purrr::map_int(
      time,
      \(current_time) sum(risk_cartoon$exit_time >= current_time)
    ),
    label = paste0("At risk at ", time, ": ", at_risk)
  )

ggplot2::ggplot(risk_cartoon) +
  ggplot2::aes(y = person_id) +
  ggplot2::geom_segment(
    ggplot2::aes(
      x = 0,
      xend = exit_time,
      yend = person_id
    ),
    linewidth = 1,
    color = "grey50"
  ) +
  ggplot2::geom_point(
    ggplot2::aes(
      x = exit_time,
      shape = status,
      fill = status
    ),
    size = 3,
    color = "black"
  ) +
  ggplot2::geom_vline(
    data = dplyr::filter(risk_counts, time > 0),
    ggplot2::aes(xintercept = time),
    linetype = "dashed",
    color = "grey85"
  ) +
  ggplot2::geom_text(
    data = risk_counts,
    ggplot2::aes(
      x = time,
      y = max(risk_cartoon$person_id) + 0.8,
      label = label
    ),
    size = 3.4,
    vjust = 0
  ) +
  ggplot2::scale_shape_manual(values = c(Event = 21, Censored = 22)) +
  ggplot2::scale_fill_manual(
```

Definition 7.1 (Risk Set)**.** For a survival study with n subjects, let T_i denote the true event time and C_i the censoring time for subject i, and let $\tilde{T}_i = \min(T_i, C_i)$ be the observed follow-up time. The **risk set at time** t is

$$\mathcal{R}(t) \stackrel{\text{def}}{=} \{i \in \{1, \dots, n\} : \tilde{T}_i \geq t\},$$

the set of subjects still under observation (neither having experienced the event nor been censored) immediately before time t.
The **number at risk at time** t is

$$r(t) \stackrel{\text{def}}{=} |\mathcal{R}(t)|.$$

At each ordered event time t_i, this count is written $r_i \stackrel{\text{def}}{=} r(t_i)$.

Exm

Example 7.1. In Figure 10, the 8-person study has $\tilde{T}_i \in \{2, 3, 4, 5, 6, 6, 7, 8\}$. At time $t = 4$, subjects 3, 4, 5, 6, 7, and 8 still have $\tilde{T}_i \geq 4$, so $\mathcal{R}(4) = \{3, 4, 5, 6, 7, 8\}$ and $r(4) = 6$.

Definition 7.2 (Kaplan-Meier Product-Limit Estimator of Survival Function)**.** If a time-to-event data set contains k event times t_i, $(i \in 1 : k)$, where r_i is the number of individuals at risk at time t_i and d_i is the number of events at time t_i, then the **Kaplan-Meier Product-Limit Estimator** of the survival function is:

$$\hat{\lambda}_i = \frac{d_i}{r_i}$$

$$\hat{\kappa}_i = 1 - \hat{\lambda}_i = \frac{r_i - d_i}{r_i}$$

$$\hat{\mathrm{S}}_{KM}(t) \stackrel{\text{def}}{=} \prod_{\{i:\ t_i \leq t\}} \hat{\kappa}_i$$

To see why multiplying the conditional survival factors estimates marginal survival, write the ordered distinct exit times as $y_1 < y_2 < \cdots < y_m$. Here Y denotes exit time (either event time or censoring time), while T denotes the underlying event time, which is not always observed.

Because y_{j-1} and y_j are consecutive distinct exit times, there are no exits between them. Therefore the conditional probability of surviving between these two times is 1:

$$\Pr(Y \geq y_j \mid Y > y_{j-1}) = 1.$$

Then the event $\{Y \geq y_j\}$ is contained in the event $\{Y > y_{j-1}\}$, because $y_j > y_{j-1}$. Therefore intersecting $\{Y \geq y_j\}$ with $\{Y > y_{j-1}\}$ does not change the event:

Theorem 7.1 (Consecutive Exit-Time Identity)**.** *If* $\Pr(Y \geq y_j \mid Y > y_{j-1}) = 1$*, then:*

$$\Pr(Y \geq y_j) = \Pr(Y > y_{j-1})$$

Proof

Proof.

$$
\begin{aligned}
&\Pr(Y \geq y_j) \\
&\qquad = \Pr(Y \geq y_j, Y > y_{j-1}) \\
&\qquad = \Pr(Y \geq y_j \mid Y > y_{j-1}) \Pr(Y > y_{j-1}) \\
&\qquad = 1 \Pr(Y > y_{j-1}) \\
&\qquad = \Pr(Y > y_{j-1})
\end{aligned}
$$

□

The first equality uses the containment $\{Y \geq y_j\} \subseteq \{Y > y_{j-1}\}$ (subset property[5]). The second equality uses the multiplication rule for probabilities, and the third equality uses the between-exit-time survival assumption.

Let $\kappa(y_j) = \Pr(Y > y_j \mid Y \geq y_j)$ denote the conditional probability of surviving past the exit time y_j, given survival up to y_j. The marginal survival through y_j can then be written recursively:

$$
\begin{aligned}
\mathrm{S}(y_j) &= \Pr(Y > y_j) \\
&= \Pr(Y > y_j, Y \geq y_j) \\
&= \Pr(Y > y_j \mid Y \geq y_j) \Pr(Y \geq y_j) \\
&= \Pr(Y > y_j \mid Y \geq y_j) \Pr(Y > y_{j-1}) \\
&= \kappa(y_j) \Pr(Y > y_{j-1}) \\
&= \kappa(y_j)\, \mathrm{S}(y_{j-1}).
\end{aligned}
$$

Here the first equality again uses the subset property[6]: if $Y > y_j$, then $Y \geq y_j$, so $\{Y > y_j\} \subseteq \{Y \geq y_j\}$. The third equality substitutes the Theorem 7.1 result, $\Pr(Y \geq y_j) = \Pr(Y > y_{j-1})$.

The same recursion can be applied repeatedly. If $S_j = \Pr(Y > y_j)$ and $S_0 = 1$, then:

$$
\begin{aligned}
S_1 &= \kappa(y_1) S_0 \\
&= \kappa(y_1), \\
S_2 &= \kappa(y_2) S_1 \\
&= \kappa(y_2)\kappa(y_1), \\
S_3 &= \kappa(y_3) S_2 \\
&= \kappa(y_3)\kappa(y_2)\kappa(y_1).
\end{aligned}
$$

Continuing in this way gives $S_j = \prod_{k=1}^{j} \kappa(y_k)$.

To estimate the survival function for the underlying event time T, we replace the conditional survival probabilities $\Pr(T > y_k \mid T \geq y_k)$ with their empirical estimates at the observed exit times. This gives the Kaplan-Meier product-limit estimator:

$$
\begin{aligned}
\hat{\Pr}(T > t) &= \hat{S}_{KM}(t) \\
&= \prod_{k:\, y_k \leq t} \hat{\Pr}(T > y_k \mid T \geq y_k) \\
&= \prod_{k:\, y_k \leq t} \hat{\kappa}_k \\
&= \prod_{k:\, y_k \leq t} \frac{r_k - d_k}{r_k}
\end{aligned}
$$

[5] probability.qmd#thm-prob-subset
[6] probability.qmd#thm-prob-subset

where r_k is the number at risk at time y_k and d_k is the number of events (not total exits) at time y_k. The empirical factor $(r_k - d_k)/r_k$ estimates $\Pr(T > y_k \mid T \geq y_k)$ by counting only events in the numerator, since censoring times do not provide information about the event time distribution.

For any time t between two consecutive exit times, the estimate stays constant, because the only additional conditional survival factors are 1.

Exercise 7.1. Table 3 lists some simulated survival data, where:

- Y is study exit time
- D is reason for study exit:
  - $D = 1$: event
  - $D = 0$: censored
- `S` is the combination of Y and D into a single `Surv()` variable.

```r
library(tibble)
data1 <- tibble(
  Y = c(1, 3, 7, 10, 13, 15, 16, 16, 16),
  D = c(1, 1, 1,  1,  0,  1,  0,  0,  0),
  S = survival::Surv(Y, D)
)
knitr::kable(data1)
```

Table 3: Simulated survival data for Exercise 7.1.

Y	D	S
1	1	1
3	1	3
7	1	7
10	1	10
13	0	13+
15	1	15
16	0	16+
16	0	16+
16	0	16+

Compute the Kaplan-Meier (KM) estimated survival curve by hand.

Solution

Solution 7.1. Let:

- n: total sample size
- y: study exit time;
- $d(y)$: number of events at y;
- $c(y)$: number exiting without events ("censored") at y;
- $e(y) = d(y) + c(y)$: total exiting at y;
- $E(y)$: cumulative exits prior to y;
- $r(y) = n - E(y)$: number at risk at y;
- $r^*(y) = r(y) - e(y)$: number at risk after y;
- $\hat{\kappa}(y) = \hat{\Pr}(T > y \mid T \geq y) = [r(y) - d(y)]/r(y)$: conditional survival factor;
- $\hat{\lambda}(y) = \hat{\Pr}(T = y \mid T \geq y) = \frac{d(y)}{r(y)} = 1 - \hat{\kappa}(y)$: estimated discrete hazard;
- $\hat{\mathrm{S}}_{KM}(y) = \prod_{k:\, y_k \leq y} \hat{\kappa}(y_k)$: Kaplan-Meier survival estimate.

```r
library(pander)
library(tidyverse)

km_curve <-
  data1 |>
  summarise(.by  = Y,
            events = sum(D == 1),
            censored = sum(D == 0)) |>
  arrange(Y) |>
  mutate(
    study_size = nrow(data1),
    exiting = events + censored,
    exited = cumsum(exiting) |> dplyr::lag(default = 0),
    at_risk = study_size - exited,
    r_star = at_risk - exiting,
    hazard = events / at_risk,
    km_factor = 1 - hazard,
    km_surv_curve = cumprod(km_factor)
  ) |>
  select(-study_size) |>
  relocate(km_factor, .before = hazard)
km_curve |>
  mutate(
    hazard_math = paste0("\\frac{", events, "}{", at_risk, "}"),
    km_factor_math = paste0("\\frac{", at_risk - events, "}{", at_risk, "}"),
    km_surv_curve = paste0(
      "$",
      purrr::map_chr(
        row_number(),
        \(i) paste(km_factor_math[seq_len(i)], collapse = " \\times ")
      ),
      " = ",
      round(km_surv_curve, 4),
      "$"
    ),
    hazard = paste0(
      "$", hazard_math, " = ",
      round(hazard, 4), "$"
    ),
    km_factor = paste0(
      "$", km_factor_math, " = ",
      round(km_factor, 4), "$"
    )
  ) |>
  select(-hazard_math, -km_factor_math) |>
  rename(
    `$y$`                        = Y,
    `$d(y)$`                     = events,
    `$c(y)$`                     = censored,
    `$e(y)$`                     = exiting,
    `$E(y)$`                     = exited,
    `$r(y)$`                     = at_risk,
    `$r^*(y)$`                   = r_star,
    `$\\hat{\\cs}(y)$`         = km_factor,
    `$\\hat{\\haz}(y)$`          = hazard,
    `$\\hsurv_{KM}(y)$`          = km_surv_curve
  ) |>
  pander()
```

Table 4: Kaplan-Meier survival curve calculations

y	$d(y)$	$c(y)$	$e(y)$	$E(y)$	$r(y)$	$r^*(y)$	$\hat{\kappa}(y)$	$\hat{\lambda}(y)$	$\hat{S}_{KM}(y)$
1	1	0	1	0	9	8	$\frac{8}{9} = 0.8889$	$\frac{1}{9} = 0.1111$	$\frac{8}{9} = 0.8889$
3	1	0	1	1	8	7	$\frac{7}{8} = 0.875$	$\frac{1}{8} = 0.125$	$\frac{8}{9} \times \frac{7}{8} = 0.7778$
7	1	0	1	2	7	6	$\frac{6}{7} = 0.8571$	$\frac{1}{7} = 0.1429$	$\frac{8}{9} \times \frac{7}{8} \times \frac{6}{7} = 0.6667$
10	1	0	1	3	6	5	$\frac{5}{6} = 0.8333$	$\frac{1}{6} = 0.1667$	$\frac{8}{9} \times \frac{7}{8} \times \frac{6}{7} \times \frac{5}{6} = 0.5556$
13	0	1	1	4	5	4	$\frac{5}{5} = 1$	$\frac{0}{5} = 0$	$\frac{8}{9} \times \frac{7}{8} \times \frac{6}{7} \times \frac{5}{6} \times \frac{5}{5} = 0.5556$
15	1	0	1	5	4	3	$\frac{3}{4} = 0.75$	$\frac{1}{4} = 0.25$	$\frac{8}{9} \times \frac{7}{8} \times \frac{6}{7} \times \frac{5}{6} \times \frac{5}{5} \times \frac{3}{4} = 0.4167$
16	0	3	3	6	3	0	$\frac{3}{3} = 1$	$\frac{0}{3} = 0$	$\frac{8}{9} \times \frac{7}{8} \times \frac{6}{7} \times \frac{5}{6} \times \frac{5}{5} \times \frac{3}{4} \times \frac{3}{3} = 0.4167$

Exercise 7.2. Implement the KM survival curve estimator in R. Check the output of your implementation against the version in the `survival` package.

Solution

Solution 7.2. See above for implementation. Here's the version from the `survival` package:

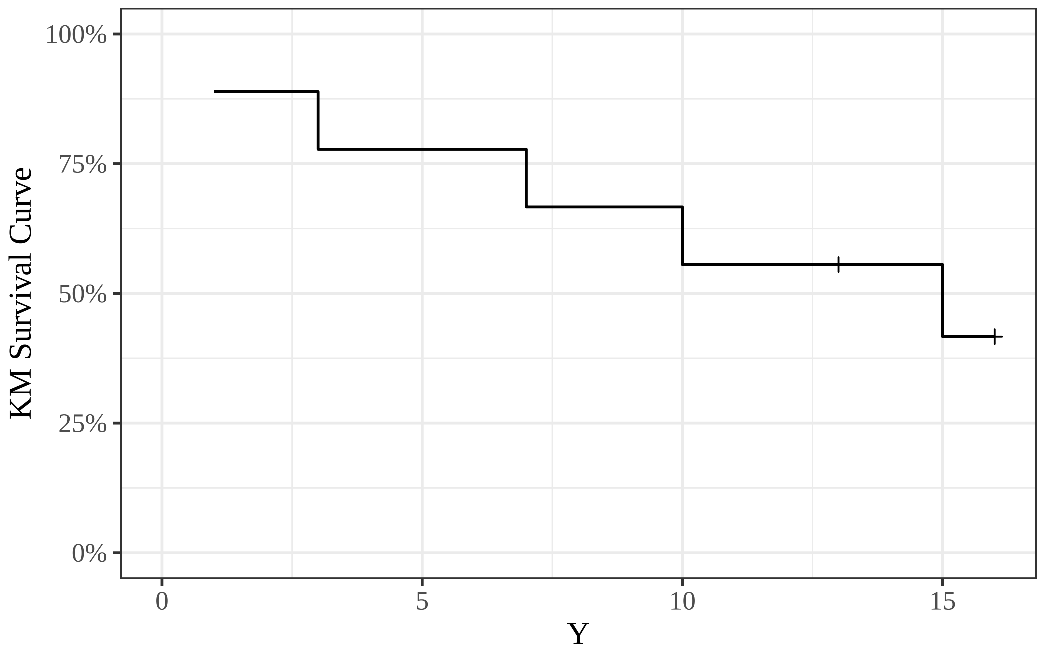
```
library(survival)
data1 |>
  survfit(Surv(time = Y, event = D) ~ 1, data = _) |>
  summary()
#> Call: survfit(formula = Surv(time = Y, event = D) ~ 1, data = data1)
#>
#>  time n.risk n.event survival std.err lower 95% CI upper 95% CI
#>     1      9       1    0.889   0.105        0.706        1.000
#>     3      8       1    0.778   0.139        0.549        1.000
#>     7      7       1    0.667   0.157        0.420        1.000
#>    10      6       1    0.556   0.166        0.310        0.997
#>    15      4       1    0.417   0.173        0.185        0.940
```

Exercise 7.3. Graph the KM estimated survival curve for the data in Table 3.

Solution

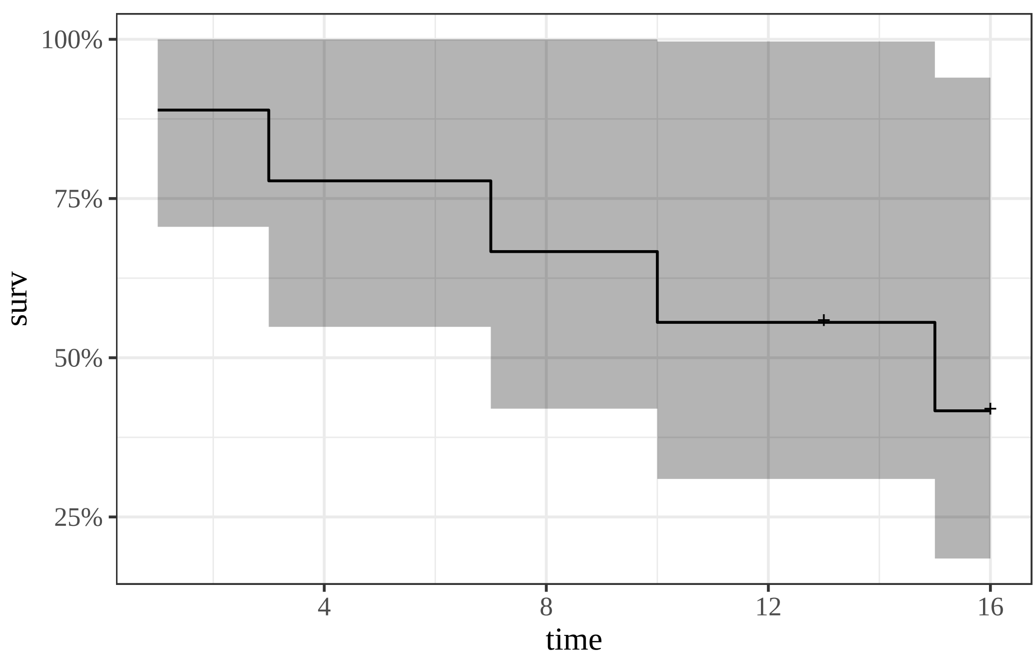
Solution 7.3.

```
library(ggplot2)
km_curve |>
  ggplot(aes(x = Y, y = km_surv_curve)) +
  geom_step() +
  geom_point(data = km_curve |> filter(censored > 0), shape = 3) +
  ylab("KM Survival Curve") +
  expand_limits(y = c(0, 1), x = 0) +
  scale_y_continuous(labels = scales::percent)
```



or

```
library(ggfortify)
data1 <- data1 |>
  mutate(
    surv = Surv(time = Y, event = D)
  )
KM_model <- data1 |> survfit(formula = surv ~ 1)
KM_model |> autoplot()
```



Exercise 7.4. Find the KM estimate of median survival time.

Solution

Solution 7.4.

```
KM_model |> quantile(prob = 0.5) |> as_tibble()
#> # A tibble: 1 x 3
#>   quantile lower upper
#>      <dbl> <dbl> <dbl>
#> 1       15     7    NA
```

Theorem 7.2 (Kaplan-Meier Estimate with No Censored Observations)**.** *If there are no censored data, and there are n data points, then just after (say) the third event time*

$$\begin{aligned}\hat{\mathrm{S}}(t) &= \prod_{t_i \le t}\left[1-\frac{d_i}{r_i}\right]\\ &= \left[\frac{n-d_1}{n}\right]\left[\frac{n-d_1-d_2}{n-d_1}\right]\left[\frac{n-d_1-d_2-d_3}{n-d_1-d_2}\right]\\ &= \frac{n-d_1-d_2-d_3}{n}\\ &= 1-\frac{d_1+d_2+d_3}{n}\\ &= 1-\hat{F}(t)\end{aligned}$$

where $\hat{F}(t)$ is the usual empirical CDF estimate.

7.3 Variance of the Kaplan-Meier estimator

The estimated variance of $\hat{\mathrm{S}}(t)$ at a single time point t is given by **Greenwood's formula**:

Theorem 7.3 (Greenwood's estimator for variance of Kaplan-Meier survival estimator)**.**

$$\widehat{\mathrm{Var}}\left(\hat{\mathrm{S}}(t)\right) = \hat{\mathrm{S}}(t)^2 \sum_{t_i \le t} \frac{d_i}{r_i(r_i-d_i)} \tag{3}$$

(Klein and Moeschberger 2003, sec. 4.2, eq. (4.2.2))

We can use Equation 3 for confidence intervals for a survival function or a difference of survival functions.

7.3.1 Understanding Greenwood's formula (optional)

To see where Greenwood's formula comes from, let $x_i = r_i - d_i$. We approximate the solution treating each time as independent, with r_i fixed and ignore randomness in times of failure and we treat x_i as independent binomials $\mathrm{Bin}(r_i, p_i)$. Letting $\mathrm{S}(t)$ be the "true" survival function

$$\begin{aligned}\hat{\mathrm{S}}(t) &= \prod_{t_i \le t} x_i/r_i\\ \mathrm{S}(t) &= \prod_{t_i \le t} p_i\end{aligned}$$

$$
\begin{aligned}
\frac{\hat{\mathrm{S}}(t)}{\mathrm{S}(t)} &= \prod_{t_i \le t} \frac{x_i}{p_i r_i} \\
&= \prod_{t_i \le t} \frac{\hat{p}_i}{p_i} \\
&= \prod_{t_i \le t} \left(1 + \frac{\hat{p}_i - p_i}{p_i}\right) \\
&\approx 1 + \sum_{t_i \le t} \frac{\hat{p}_i - p_i}{p_i}
\end{aligned}
$$

$$
\begin{aligned}
\mathrm{Var}\left(\frac{\hat{\mathrm{S}}(t)}{\mathrm{S}(t)}\right) &\approx \mathrm{Var}\left(1 + \sum_{t_i \le t} \frac{\hat{p}_i - p_i}{p_i}\right) \\
&= \sum_{t_i \le t} \frac{1}{p_i^2} \frac{p_i(1-p_i)}{r_i} \\
&= \sum_{t_i \le t} \frac{(1-p_i)}{p_i r_i} \\
&\approx \sum_{t_i \le t} \frac{(1 - x_i/r_i)}{x_i} \\
&= \sum_{t_i \le t} \frac{r_i - x_i}{x_i r_i} \\
&= \sum_{t_i \le t} \frac{d_i}{r_i(r_i - d_i)} \\
\therefore \mathrm{Var}\left(\hat{\mathrm{S}}(t)\right) &\approx \hat{\mathrm{S}}(t)^2 \sum_{t_i \le t} \frac{d_i}{r_i(r_i - d_i)}
\end{aligned}
$$

Exm

Example 7.2 (Kaplan-Meier curve for `drug6mp` data)**.** Here is the Kaplan-Meier estimated survival curve for the patients who received 6-MP in the `drug6mp` dataset (we will see code to produce figures like this one shortly):

```r
library(KMsurv)
data(drug6mp)
library(dplyr)
library(survival)

km_model1 <-
  drug6mp |>
  mutate(surv = Surv(t2, relapse)) |>
  survfit(formula = surv ~ 1, data = _)

library(ggfortify)
km_model1 |>
  autoplot(
    mark.time = TRUE,
    conf.int = FALSE
  ) +
  expand_limits(y = 0) +
  xlab("Time since diagnosis (months)") +
  ylab("KM Survival Curve")
```

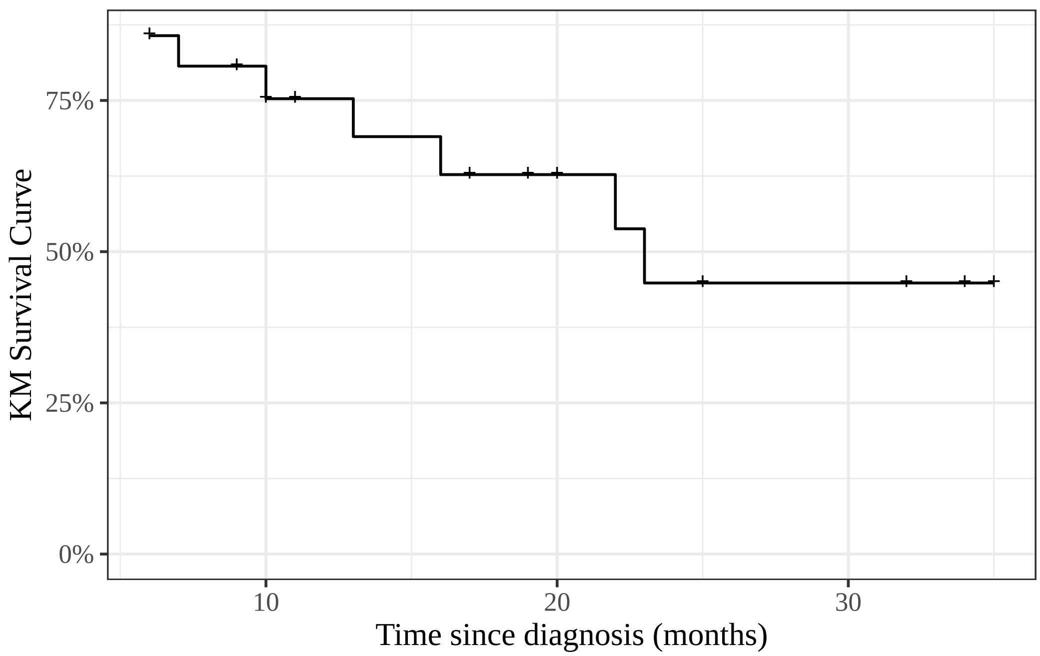


Figure 11: Kaplan-Meier Survival Curve for 6-MP Patients

7.4 Kaplan-Meier calculations

Let's compute these estimates and build the chart by hand:

```r
library(KMsurv)
library(dplyr)
data(drug6mp)

data_v2 <-
  drug6mp |>
  as_tibble() |>
  mutate(
    remstat = remstat |>
      case_match(
```

```r
        1 ~ "partial",
        2 ~ "complete"
      ),
    # renaming to "outcome" while relabeling is just a style choice:
    outcome = relapse |>
      case_match(
        0 ~ "censored",
        1 ~ "relapsed"
      )
  )

km_table <-
  data_v2 |>
  summarize(
    .by = t2,
    Relapses = sum(outcome == "relapsed"),
    Censored = sum(outcome == "censored")
  ) |>
  # here we add a start time row, so the graph starts at time 0:
  bind_rows(
    tibble(
      t2 = 0,
      Relapses = 0,
      Censored = 0
    )
  ) |>
  # sort in time order:
  arrange(t2) |>
  mutate(
    Exiting = Relapses + Censored,
    `Study Size` = sum(Exiting),
    Exited = cumsum(Exiting) |> dplyr::lag(default = 0),
    `At Risk` = `Study Size` - Exited,
    Hazard = Relapses / `At Risk`,
    `KM Factor` = 1 - Hazard,
    `Cumulative Hazard` = cumsum(`Hazard`),
    `KM Survival Curve` = cumprod(`KM Factor`)
  )

library(pander)
pander(km_table)
```

t2	Relapses	Censored	Exiting	Study Size	Exited	At Risk	Hazard	KM Factor	Cumulative Hazard	KM Survival Curve
0	0	0	0	21	0	21	0	1	0	1
6	3	1	4	21	0	21	0.1429	0.8571	0.1429	0.8571
7	1	0	1	21	4	17	0.05882	0.9412	0.2017	0.8067
9	0	1	1	21	5	16	0	1	0.2017	0.8067
10	1	1	2	21	6	15	0.06667	0.9333	0.2683	0.7529
11	0	1	1	21	8	13	0	1	0.2683	0.7529
13	1	0	1	21	9	12	0.08333	0.9167	0.3517	0.6902
16	1	0	1	21	10	11	0.09091	0.9091	0.4426	0.6275
17	0	1	1	21	11	10	0	1	0.4426	0.6275
19	0	1	1	21	12	9	0	1	0.4426	0.6275
20	0	1	1	21	13	8	0	1	0.4426	0.6275
22	1	0	1	21	14	7	0.1429	0.8571	0.5854	0.5378

t2	Re-lapses	Cen-sored	Exit-ing	Study Size	Ex-ited	At Risk	Haz-ard	KM Factor	Cumula-tive Hazard	KM Survival Curve
23	1	0	1	21	15	6	0.1667	0.8333	0.7521	0.4482
25	0	1	1	21	16	5	0	1	0.7521	0.4482
32	0	2	2	21	17	4	0	1	0.7521	0.4482
34	0	1	1	21	19	2	0	1	0.7521	0.4482
35	0	1	1	21	20	1	0	1	0.7521	0.4482

7.4.1 Summary

For the 6-MP patients at time 6 months, there are 21 patients at risk. At $t = 6$ there are 3 relapses and 1 censored observations.

The Kaplan-Meier factor is $(21 - 3)/21 = 0.857$. The number at risk for the next time ($t = 7$) is $21 - 3 - 1 = 17$.

At time 7 months, there are 17 patients at risk. At $t = 7$ there is 1 relapse and 0 censored observations. The Kaplan-Meier factor is $(17-1)/17 = 0.941$. The Kaplan Meier estimate is $0.857 \times 0.941 = 0.807$. The number at risk for the next time ($t = 9$) is $17 - 1 = 16$.

Now, let's graph this estimated survival curve using `ggplot()`:

```
library(ggplot2)
conflicts_prefer(dplyr::filter)
km_table |>
  ggplot(aes(x = t2, y = `KM Survival Curve`)) +
  geom_step() +
  geom_point(data = km_table |> filter(Censored > 0), shape = 3) +
  expand_limits(y = c(0, 1), x = 0) +
  xlab("Time since diagnosis (months)") +
  ylab("KM Survival Curve") +
  scale_y_continuous(labels = scales::percent)
```

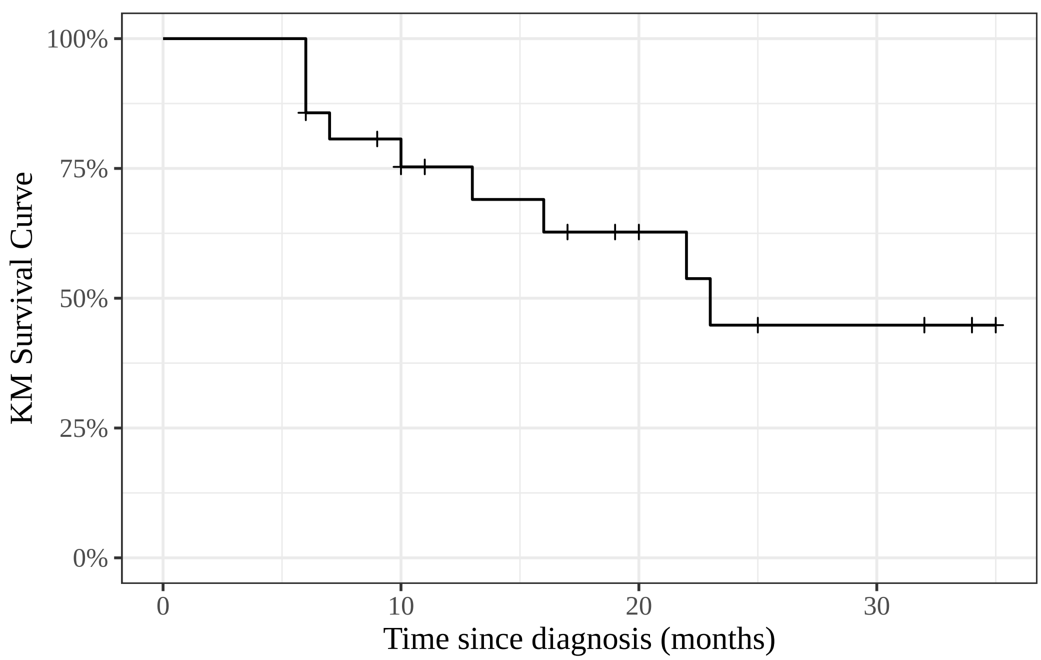


Figure 12: KM curve for 6MP patients, calculated by hand

Exercise 7.5 (Construct a prediction interval)**.** Suppose a cancer patient is predicted to have an expected (mean) lifetime of 7 years after diagnosis, and suppose the distribution is exponential.
Construct a 95% prediction interval for survival.

Tip

Use the quantiles of the exponential distribution.

Solution

Solution 7.5. If the mean is 7 years until death, then the rate parameter $\lambda = 1/7$ events (deaths) per year.
The 0.025 quantile of the exponential distribution with $\lambda = 1/7$ is `qexp(p 0.025, rate = 1/7)` $= 0.177225$ and the 0.975 quantile is `qexp(p 0.975, rate = 1/7)` $= 25.822156$, so the prediction interval is `qexp(p c(.025, 0.975), rate = 1/7)` $= (0.177225, 25.822156)$.

Exercise 7.6. Graph the prediction interval as a function of the mean, for Gaussian ($\sigma = 1$), Binomial, Poisson, and Exponential.

Solution

Solution 7.6. Left to the reader for now.

Exercise 7.7 (Explain the results)**.** Why do time-to-event models have such wide predictive intervals?

Tip

Consider the relationship between the mean, variance, and standard deviation of the exponential distribution, and contrast that relationship with the Poisson distribution and the Bernoulli distribution.

Solution

Solution 7.7. In the exponential distribution, variance is the square of the mean (hence SD is equal to mean); as opposed to Poisson, where variance was equal to the mean (and SD is the square-root of the mean), or the Bernoulli, where the variance is the mean minus the square of the mean (so the SD is smaller than the square-root of the mean).

8 Using the `survival` package in R

We don't have to do these calculations by hand every time; the `survival` package and several others have functions available to automate many of these tasks (full list: https://cran.r-project.org/web/views/Survival.html).

8.1 The Surv function

To use the `survival` package, the first step is telling R how to combine the exit time and exit reason (censoring versus event) columns. The `Surv()` function accomplishes this task.

Exm

Example 8.1 (`Surv()` with `drug6mp` data).

```
library(survival)
data_v3 <-
  data_v2 |>
  mutate(
    surv2 = Surv(
      time = t2,
      event = (outcome == "relapsed")
    )
  )

print(data_v3)
#> # A tibble: 21 x 7
#>     pair remstat    t1    t2 relapse outcome   surv2
#>    <int> <chr>   <int> <int>   <int> <chr>    <Surv>
#>  1     1 partial     1    10       1 relapsed    10
#>  2     2 complete   22     7       1 relapsed     7
#>  3     3 complete    3    32       0 censored    32+
#>  4     4 complete   12    23       1 relapsed    23
#>  5     5 complete    8    22       1 relapsed    22
#>  6     6 partial    17     6       1 relapsed     6
#>  7     7 complete    2    16       1 relapsed    16
#>  8     8 complete   11    34       0 censored    34+
#>  9     9 complete    8    32       0 censored    32+
#> 10    10 complete   12    25       0 censored    25+
#> # i 11 more rows
```

The output of `Surv()` is a vector of objects with class `Surv`. When we print this vector:

- observations where the event was observed are printed as the event time (for example, `surv2 = 10` on line 1)
- observations where the event was right-censored are printed as the censoring time with a plus sign (`+`; for example, `surv2 = 32+` on line 3).

8.2 The survfit function

Once we have constructed our `Surv` variable, we can calculate the Kaplan-Meier estimate of the survival curve using the `survfit()` function.

Note

The documentation for `?survfit` isn't too helpful; the `survfit.formula` documentation is better.

Exm

Example 8.2 (`survfit()` with `drug6mp` data). Here we use `survfit()` to create a `survfit` object, which contains the Kaplan-Meier estimate:

```r
km_model <- survfit(
  formula = surv2 ~ 1,
  data = data_v3
)
```

`print.survfit()` just gives some summary statistics:

```r
print(km_model)
#> Call: survfit(formula = surv2 ~ 1, data = data_v3)
#>
#>       n events median 0.95LCL 0.95UCL
#> [1,] 21      9     23      16      NA
```

`summary.survfit()` shows us the underlying Kaplan-Meier table:

```r
summary(km_model)
#> Call: survfit(formula = surv2 ~ 1, data = data_v3)
#>
#>  time n.risk n.event survival std.err lower 95% CI upper 95% CI
#>     6     21       3    0.857  0.0764        0.720        1.000
#>     7     17       1    0.807  0.0869        0.653        0.996
#>    10     15       1    0.753  0.0963        0.586        0.968
#>    13     12       1    0.690  0.1068        0.510        0.935
#>    16     11       1    0.627  0.1141        0.439        0.896
#>    22      7       1    0.538  0.1282        0.337        0.858
#>    23      6       1    0.448  0.1346        0.249        0.807
```

We can specify which time points we want using the `times` argument:

```r
summary(
  km_model,
  times = c(0, data_v3$t2)
)
#> Call: survfit(formula = surv2 ~ 1, data = data_v3)
#>
#>  time n.risk n.event survival std.err lower 95% CI upper 95% CI
#>     0     21       0    1.000  0.0000        1.000        1.000
#>    10     15       1    0.753  0.0963        0.586        0.968
#>     7     17       1    0.807  0.0869        0.653        0.996
#>    32      4       0    0.448  0.1346        0.249        0.807
#>    23      6       1    0.448  0.1346        0.249        0.807
#>    22      7       1    0.538  0.1282        0.337        0.858
#>     6     21       3    0.857  0.0764        0.720        1.000
#>    16     11       1    0.627  0.1141        0.439        0.896
#>    34      2       0    0.448  0.1346        0.249        0.807
#>    32      4       0    0.448  0.1346        0.249        0.807
#>    25      5       0    0.448  0.1346        0.249        0.807
#>    11     13       0    0.753  0.0963        0.586        0.968
#>    20      8       0    0.627  0.1141        0.439        0.896
#>    19      9       0    0.627  0.1141        0.439        0.896
#>     6     21       3    0.857  0.0764        0.720        1.000
#>    17     10       0    0.627  0.1141        0.439        0.896
#>    35      1       0    0.448  0.1346        0.249        0.807
#>     6     21       3    0.857  0.0764        0.720        1.000
#>    13     12       1    0.690  0.1068        0.510        0.935
#>     9     16       0    0.807  0.0869        0.653        0.996
#>     6     21       3    0.857  0.0764        0.720        1.000
#>    10     15       1    0.753  0.0963        0.586        0.968
```

```r
?summary.survfit
```

8.3 Plotting estimated survival functions

We can plot `survfit` objects with `plot()`, `autoplot()`, or `ggsurvplot()`:

```
library(ggfortify)
autoplot(km_model)
```

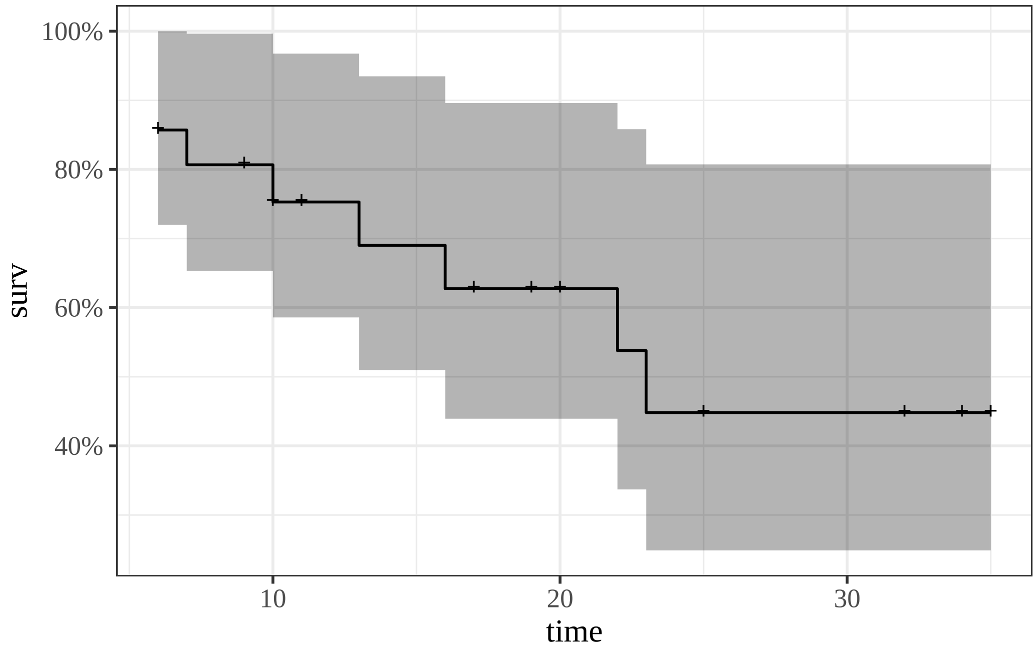


Figure 13: Kaplan-Meier Survival Curve for 6-MP Patients

8.3.1 quantiles of survival curve

We can extract quantiles with `quantile()`:

```
km_model |>
  quantile(p = c(.25, .5)) |>
  as_tibble() |>
  mutate(p = c(.25, .5)) |>
  relocate(p, .before = everything())
#> # A tibble: 2 x 4
#>       p quantile lower upper
#>   <dbl>    <dbl> <dbl> <dbl>
#> 1  0.25       13     6    NA
#> 2  0.5        23    16    NA
```

8.4 R Packages Ecosystem for Survival Analysis

R provides a rich ecosystem of packages for survival analysis, ranging from core functionality to specialized visualization tools and advanced modeling capabilities.

8.4.1 Visualization Packages

ggsurvfit

`ggsurvfit`[7] is a modern package for creating publication-ready survival plots using ggplot2.

- Developed by Daniel D. Sjoberg[8] and collaborators

[7] https://danieldsjoberg.com/ggsurvfit/
[8] https://www.danieldsjoberg.com/

- Seamlessly integrates with ggplot2, allowing full customization using familiar ggplot2 syntax
- Key features:
  - Create Kaplan-Meier plots with `ggsurvfit()`
  - Add confidence intervals with `add_confidence_interval()`
  - Add risk tables with `add_risktable()`
  - Add quantile annotations with `add_quantile()`
  - Support for competing risks with `ggcuminc()`
- Produces publication-ready legends without showing raw variable names
- All plot elements are native ggplot2 layers, making customization straightforward
- Available on CRAN[9] and GitHub[10]

survminer

`survminer`[11] is another popular visualization package for survival analysis.

- Creates ggplot2-based survival plots using `ggsurvplot()`
- Provides functions for visualizing Cox model results
- Includes tools for testing proportional hazards assumptions
- Offers built-in themes and color palettes for publication-quality plots
- Can display risk tables, cumulative events, and censoring counts

ggfortify

`ggfortify`[12] extends ggplot2 with automatic plotting capabilities.

- Provides `autoplot()` method for `survfit` objects (demonstrated in the plotting example above)
- One-line code to create survival curves with confidence intervals
- Automatically handles grouping variables and creates legends
- Shows censoring marks on plots by default
- Returns ggplot2 objects for further customization
- Also supports many other statistical objects beyond survival analysis

8.4.2 Additional Modeling Packages

Several packages extend the modeling capabilities beyond the core `survival` package:

- **`flexsurv`**[13]: Flexible parametric survival models with a wide range of distributions
- **`rms`**[14] (Regression Modeling Strategies): Advanced regression modeling including survival models with tools for model validation and calibration
- **`cmprsk`**[15]: Competing risks regression using the Fine-Gray model
- **`mstate`**[16]: Multi-state survival models for complex event histories
- **`timereg`**[17]: Flexible regression models for survival data, including additive hazards models
- **`frailtypack`**[18]: Frailty models for clustered or recurrent event data
- **`riskRegression`**[19]: Risk prediction models and performance evaluation
- **`pec`**[20]: Prediction error curves for survival model validation
- **`prodlim`**[21]: Fast estimation of survival models including competing risks

[9] https://cran.r-project.org/web/packages/ggsurvfit/index.html
[10] https://github.com/pharmaverse/ggsurvfit
[11] https://cran.r-project.org/web/packages/survminer/index.html
[12] https://cran.r-project.org/web/packages/ggfortify/index.html
[13] https://cran.r-project.org/web/packages/flexsurv/index.html
[14] https://cran.r-project.org/web/packages/rms/index.html
[15] https://cran.r-project.org/web/packages/cmprsk/index.html
[16] https://cran.r-project.org/web/packages/mstate/index.html
[17] https://cran.r-project.org/web/packages/timereg/index.html
[18] https://cran.r-project.org/web/packages/frailtypack/index.html
[19] https://cran.r-project.org/web/packages/riskRegression/index.html
[20] https://cran.r-project.org/web/packages/pec/index.html
[21] https://cran.r-project.org/web/packages/prodlim/index.html

8.4.3 Package Selection Guidance

For most standard survival analyses:

- Use **`survival`** for core functionality (Kaplan-Meier, Cox models, parametric models)
- Choose **`ggsurvfit`** for modern, customizable survival plots if you're familiar with ggplot2
- Consider **`survminer`** as an alternative visualization package with many built-in features
- Use **`ggfortify`** if you want quick, automatic plots with minimal code

For specialized analyses:

- **Competing risks**: `cmprsk` or `riskRegression`
- **Multi-state models**: `mstate`
- **Flexible parametric models**: `flexsurv`
- **Clustered/recurrent events**: `frailtypack`
- **Model validation**: `rms` or `pec`

The CRAN Survival Analysis Task View[22] provides the most comprehensive and up-to-date list of available packages.

9 The log-rank test

(a.k.a. the Mantel-Cox test)

> **Exercise 9.1.** How do we test the null hypothesis that two or more groups have the same time-to-event distribution?

> Solution
>
> *Solution* 9.1. One option is the **log-rank test**, which compares the Kaplan-Meier estimates of the survival functions of those groups.

Adapted from (Kleinbaum and Klein 2012, sec. IV, pp. 67–68):

- The log-rank test is a large-sample chi-square test.
- The log-rank test uses a test statistic that compares KM curves between groups across all survival times.
- Like many other statistics used in chi-square tests, the log-rank statistic compares observed versus expected cell counts over categories of outcomes.
- The categories for the log-rank statistic are defined by each of the ordered failure times for the entire set of data being analyzed.

9.1 Notation

Suppose we are comparing $G \geq 2$ groups, indexed by $g = 1, \dots, G$. Pool the failure times across all groups and let

- $t_1 < t_2 < \cdots < t_k$ be the **distinct ordered failure times** in the pooled data ($i = 1, \dots, k$ indexes these times).

For each ordered failure time t_i and each group g, define:

[22] https://cran.r-project.org/web/views/Survival.html

Symbol	Meaning
d_{gi}	number of failures in group g at time t_i
r_{gi}	number at risk in group g just before time t_i
$d_i = \sum_{g=1}^{G} d_{gi}$	total failures at t_i (pooled across groups)
$r_i = \sum_{g=1}^{G} r_{gi}$	total at risk at t_i (pooled across groups)

This matches the (d_i, r_i) notation used for the Kaplan-Meier estimator elsewhere in this chapter; here we additionally split each count by group.

Kleinbaum (2012, 67–69) uses m_{if} and n_{if} in place of d_{gi} and r_{gi}; we changed letters here to stay consistent with the (d_i, r_i) already used throughout this chapter.

9.2 Expected counts under the null

The null hypothesis is

$$H_0 : \text{ all } G \text{ groups have the same survival function.}$$

Under H_0, the pooled marginal hazard estimate at time t_i is

$$\hat{\lambda}_i = \frac{d_i}{r_i}.$$

The **expected** number of failures in group g at time t_i under H_0 is the pooled hazard applied to that group's risk set (Kleinbaum and Klein 2012, 68, "expected-cell-counts" box):

$$e_{gi} = r_{gi}\,\hat{\lambda}_i = \underbrace{\frac{r_{gi}}{r_i}}_{\text{fraction at risk}} \cdot \underbrace{d_i}_{\text{total failures}} \tag{4}$$

The **summed observed minus expected score** for group g over all failure times is:

$$O_g - E_g \stackrel{\text{def}}{=} \sum_{i=1}^{k} (d_{gi} - e_{gi}).$$

9.3 Log-rank statistic (two groups)

For two groups ($G = 2$), the observed-minus-expected scores satisfy $O_1 - E_1 = -(O_2 - E_2)$ (the total failures at each t_i are by definition partitioned across the two groups), so it does not matter which group we use to form the test statistic.

Theorem 9.1 (Log-rank statistic, two groups)**.** *For either $g \in \{1, 2\}$,*

$$\chi^2_{LR} = \frac{(O_g - E_g)^2}{\widehat{\operatorname{Var}(O_g - E_g)}} \stackrel{H_0}{\sim} \chi^2_1 \tag{5}$$

where r_{1i} and r_{2i} are the at-risk counts for groups 1 and 2 at time t_i (i.e., r_{gi} from Section 9.1 for $g = 1, 2$), and the variance estimate is

$$\widehat{\operatorname{Var}(O_g - E_g)} = \sum_{i=1}^{k} \frac{r_{1i}\, r_{2i}\, d_i\, (r_i - d_i)}{r_i^2\, (r_i - 1)}. \tag{6}$$

For two groups, the variance is the same whether computed for group 1 or group 2. (Kleinbaum and Klein 2012, 69–70, two-group variance formula)

Equation 6 is the hypergeometric variance for the count of failures from group 1 at t_i conditional on (d_i, r_{1i}, r_{2i}), summed over failure times. Each summand has the form $r_{1i}r_{2i}d_i(r_i - d_i)/[r_i^2(r_i - 1)]$.

9.4 Log-rank statistic (more than two groups)

For $G \geq 2$ groups, the log-rank statistic still uses the observed-minus-expected scores $O_g - E_g$, but the variance–covariance matrix of the vector $\mathbf{O} - \mathbf{E} \overset{\text{def}}{=} (O_1 - E_1, \ldots, O_G - E_G)'$ is nontrivial because the scores are linearly dependent ($\sum_g (O_g - E_g) = 0$). The statistic takes the matrix-quadratic form

$$\chi^2_{\text{LR}} \;=\; (\mathbf{O} - \mathbf{E})' \,\widehat{\Sigma}^{-}\, (\mathbf{O} - \mathbf{E}) \;\overset{H_0}{\sim}\; \chi^2_{G-1}$$

where $\widehat{\Sigma}$ is the estimated variance–covariance matrix of $\mathbf{O} - \mathbf{E}$ and $\widehat{\Sigma}^{-}$ is a generalized inverse (any $G - 1$ of the rows/columns suffice, since the scores sum to zero).

(Kleinbaum and Klein 2012, 71–72 and Chapter 2 Appendix for the matrix formula)

In practice we don't compute this by hand — every standard survival package (`survival::survdiff` in R, `sts test` in Stata, `LIFETEST` in SAS) returns the exact log-rank statistic.

9.5 Approximate (Pearson-style) statistic

When only (O_g, E_g) are available — e.g., from a printed summary — the variance–covariance matrix can be replaced by the diagonal E_g entries to yield the classic Pearson-style approximation:

$$X^2 \;\approx\; \sum_{g=1}^{G} \frac{(O_g - E_g)^2}{E_g}.$$

This is what some textbooks call "the log-rank test"; it is approximately equal to the exact statistic.

(Kleinbaum and Klein 2012, 70 (approximate formula))

9.6 The `survdiff` function

```
?survdiff
```

Exm

Example 9.1 (`survdiff()` with `drug6mp` data)**.** Now we are going to compare the placebo and 6-MP data. We need to reshape the data to make it usable with the standard `survival` workflow:

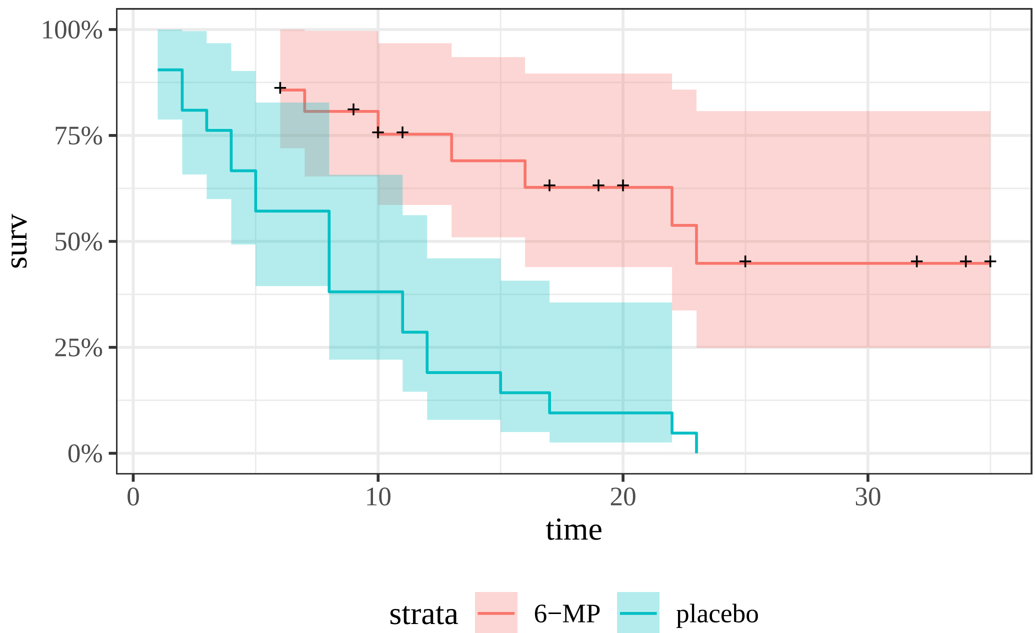
```r
library(survival)
library(tidyr)
data_v4 <-
  data_v3 |>
  select(pair, remstat, t1, t2, outcome) |>
  # here we are going to change the data from a wide format to long:
  pivot_longer(
    cols = c(t1, t2),
    names_to = "treatment",
    values_to = "exit_time"
  ) |>
  mutate(
    treatment = treatment |>
      case_match(
        "t1" ~ "placebo",
        "t2" ~ "6-MP"
      ),
    outcome = if_else(
      treatment == "placebo",
      "relapsed",
      outcome
    ),
    surv = Surv(
      time = exit_time,
      event = (outcome == "relapsed")
    )
  )
```

Using this long data format, we can fit a Kaplan-Meier curve for each treatment group simultaneously:

```r
km_model2 <-
  survfit(
    formula = surv ~ treatment,
    data = data_v4
  )
```

We can plot the curves in the same graph:

```r
km_model2 |> autoplot()
```



We can also perform something like a t-test, where the null hypothesis is that the curves are the same. The table below shows the per-time (d_{gi}, r_{gi}) counts and the expected counts e_{gi} from Equation 4:

Table 5: Observed and expected event counts for the 6-MP data, for the log-rank test. Columns: `exit_time` is t_i; `n_at_risk_placebo`/`n_at_risk_6-MP` are r_{gi}; `n_events_placebo`/`n_events_6-MP` are d_{gi}; `n_at_risk`/`n_events` are pooled r_i, d_i; `marginal_hazard` is $\hat{\lambda}_i = d_i/r_i$; `expected_*` are e_{gi} from Equation 4; `diff_*` are the per-time contributions $d_{gi} - e_{gi}$ to $O_g - E_g$.

```
o_e <- data_v4 |>
  arrange(exit_time) |>
  mutate(
    .by = treatment,
    n_exited = row_number(),
    n_at_risk = n() - n_exited + 1
  ) |>
  dplyr::summarize(
    .by = all_of(c("exit_time", "treatment")),
    n_at_risk = max(n_at_risk),
    n_events = sum(outcome == "relapsed")
  ) |>
  tidyr::pivot_wider(
    names_from = "treatment",
    values_from = c(n_at_risk, n_events)
  ) |>
  tidyr::fill(
    starts_with("n_at_risk"),
    .direction = "up"
  ) |>
  replace_na(list("n_events_placebo" = 0,
                  "n_events_6-MP" = 0)) |>
  mutate(
    n_at_risk = rowSums(across(starts_with("n_at_risk"))),
    n_events = rowSums(across(starts_with("n_events"))),
    marginal_hazard = n_events / n_at_risk,
    expected_6mp = marginal_hazard * `n_at_risk_6-MP`,
    expected_plc = marginal_hazard * n_at_risk_placebo,
    diff_6mp = `n_events_6-MP` - expected_6mp,
    diff_plc = n_events_placebo - expected_plc
  ) |>
  filter(n_events > 0)

o_e
#> # A tibble: 17 x 12
#>    exit_time n_at_risk_placebo `n_at_risk_6-MP` n_events_placebo `n_events_6-MP`
#>        <int>             <dbl>            <dbl>            <int>           <int>
#>  1         1                21               21                2               0
#>  2         2                19               21                2               0
#>  3         3                17               21                1               0
#>  4         4                16               21                2               0
#>  5         5                14               21                2               0
#>  6         6                12               21                0               3
#>  7         7                12               17                0               1
#>  8         8                12               16                4               0
#>  9        10                 8               15                0               1
#> 10        11                 8               13                2               0
#> 11        12                 6               12                2               0
#> 12        13                 4               12                0               1
#> 13        15                 4               11                1               0
#> 14        16                 3               11                0               1
#> 15        17                 3               10                1               0
#> 16        22                 2                7                1               1
#> 17        23                 1                6                1               1
#> # i 7 more variables: n_at_risk <dbl>, n_events <dbl>, marginal_hazard <dbl>,
#> #   expected_6mp <dbl>, expected_plc <dbl>, diff_6mp <dbl>, diff_plc <dbl>
```

The summed observed O_g and expected E_g totals (one row, one column per group):

```
o_e_summ <- o_e |>
  summarize(
    across(starts_with("expected"), sum),
    across(starts_with("n_events_"), sum)
  )
pander::pander(o_e_summ)
```

Table 6: Sums of observed and expected events for the 6-MP data.

expected_6mp	expected_plc	n_events_placebo	n_events_6-MP
19.25	10.75	21	9

The Pearson-style approximation to Equation 5 is

$$X^2 \approx \sum_g \frac{(O_g - E_g)^2}{E_g}$$

which we compute directly from Table 6:

```
with(
  o_e_summ,
  tibble(
    "6mp" = (`n_events_6-MP` - expected_6mp)^2 / expected_6mp,
    "placebo" = (n_events_placebo - expected_plc)^2 / expected_plc,
    sum = `6mp` + placebo
  )
) |>
  pander::pander()
```

6mp	placebo	sum
5.458	9.775	15.23

R gives us both the exact and approximate results:

```
survdiff(
  formula = surv ~ treatment,
  data = data_v4
)
#> Call:
#> survdiff(formula = surv ~ treatment, data = data_v4)
#>
#>                    N Observed Expected (O-E)^2/E (O-E)^2/V
#> treatment=6-MP    21        9     19.3      5.46      16.8
#> treatment=placebo 21       21     10.7      9.77      16.8
#>
#>  Chisq= 16.8  on 1 degrees of freedom, p= 4e-05
```

By default, `survdiff()` ignores any pairing, but we can use `strata()` to perform something similar to a paired t-test:

```
lrank_test <- survdiff(
  formula = surv ~ treatment + strata(pair),
  data = data_v4
)
lrank_test
#> Call:
#> survdiff(formula = surv ~ treatment + strata(pair), data = data_v4)
#>
#>                    N Observed Expected (O-E)^2/E (O-E)^2/V
#> treatment=6-MP    21        9     16.5      3.41      10.7
#> treatment=placebo 21       21     13.5      4.17      10.7
#>
#>  Chisq= 10.7  on 1 degrees of freedom, p= 0.001
```

Interestingly, accounting for pairing reduces the significance of the difference.

Exm

Example 9.2 (Bone Marrow Transplant Data)**.** Data from Copelan et al. (1991)

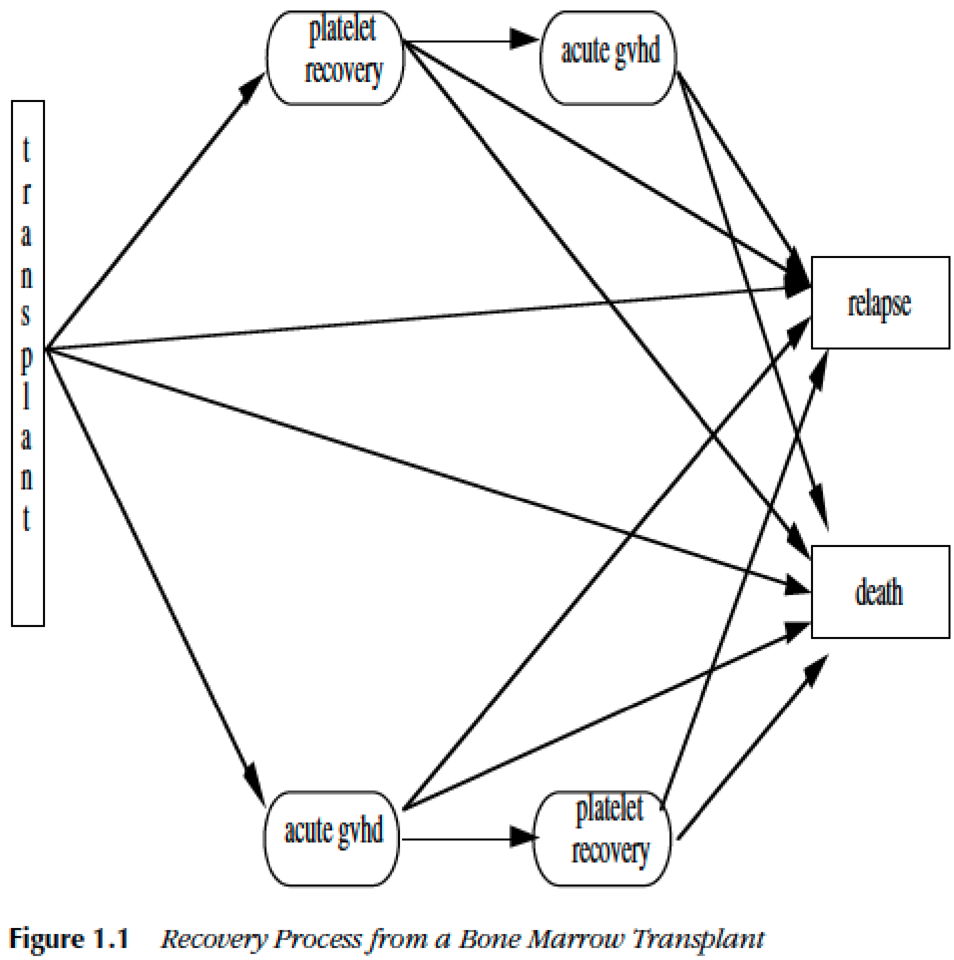


Figure 14: Recovery process from a bone marrow transplant (Fig. 1.1 from Klein and Moeschberger (2003))

Study design

Treatment

- **allogeneic** (from a donor) **bone marrow transplant therapy**

Inclusion criteria

- **acute myeloid leukemia (AML)**
- **acute lymphoblastic leukemia (ALL).**

Possible intermediate events

- **graft vs. host disease (GVHD)**: an immunological rejection response to the transplant
- **platelet recovery**: a return of platelet count to normal levels.

One or the other, both in either order, or neither may occur.

End point events

- relapse of the disease
- death

Any or all of these events may be censored.

`KMsurv::bmt` data in R

```r
library(KMsurv)
?bmt
```

Analysis plan

- We concentrate for now on disease-free survival (`t2` and `d3`) for the three risk groups, ALL, AML Low Risk, and AML High Risk.
- We will construct the Kaplan-Meier survival curves, compare them, and test for differences.
- We will construct the cumulative hazard curves and compare them.
- We will estimate the hazard functions, interpret, and compare them.

Kaplan-Meier survival curves

```
library(KMsurv)
library(survival)
data(bmt)

bmt <-
  bmt |>
  as_tibble() |>
  mutate(
    group = group |>
      factor(
        labels = c("ALL", "Low Risk AML", "High Risk AML")
      ),
    surv = Surv(t2, d3)
  )

km_model1 <- survfit(
  formula = surv ~ group,
  data = bmt
)
```

```
library(ggfortify)
autoplot(
  km_model1,
  conf.int = TRUE,
  ylab = "Pr(disease-free survival)",
  xlab = "Time since transplant (days)"
) +
  theme_bw() +
  theme(legend.position = "bottom")
```

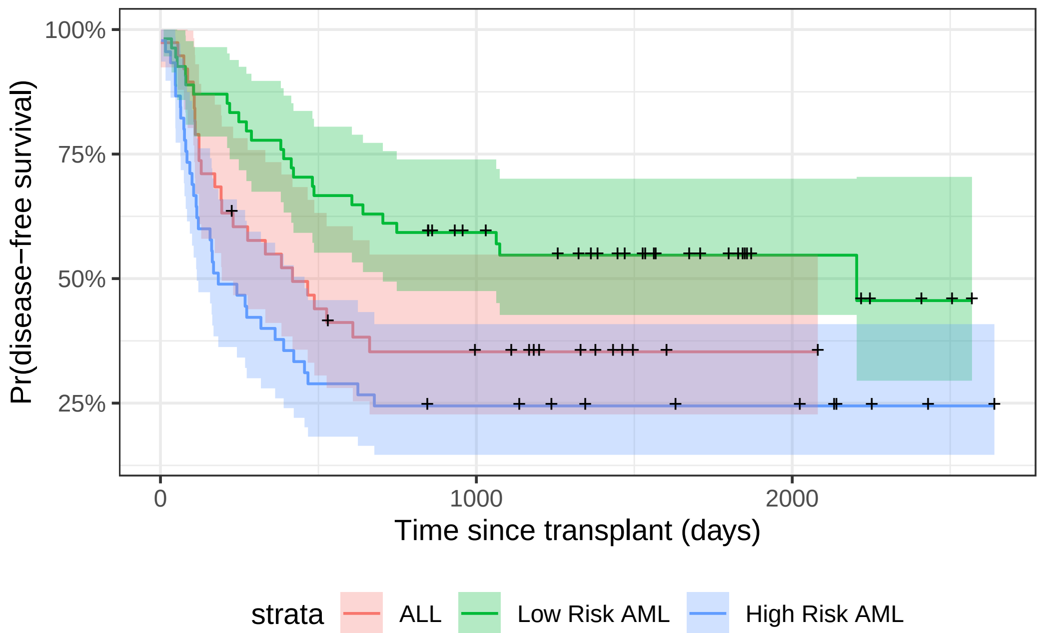


Figure 15: Disease-Free Survival by Disease Group

Test for differences among the disease groups
Here we compute a chi-square test for assocation between disease group (`group`) and disease-free survival:

```
survdiff(surv ~ group, data = bmt)
#> Call:
#> survdiff(formula = surv ~ group, data = bmt)
#>
#>                      N Observed Expected (O-E)^2/E (O-E)^2/V
#> group=ALL           38       24     21.9     0.211     0.289
#> group=Low Risk AML  54       25     40.0     5.604    11.012
#> group=High Risk AML 45       34     21.2     7.756    10.529
#>
#>  Chisq= 13.8  on 2 degrees of freedom, p= 0.001
```

Cumulative Hazard Curves for Bone-Marrow Transplant (`bmt`) data
The cumulative hazard $\Lambda(t)$ is defined in Definition 4.7, and the Kaplan-Meier (product-limit) estimator $\hat{\Lambda}(t) = -\log\left\{\hat{\mathrm{S}}(t)\right\}$ is discussed in Section 10 alongside the Nelson-Aalen estimator.

```
autoplot(
  fun = "cumhaz",
  km_model1,
  conf.int = FALSE,
  ylab = "Cumulative hazard (disease-free survival)",
  xlab = "Time since transplant (days)"
) +
  theme_bw() +
  theme(legend.position = "bottom")
```

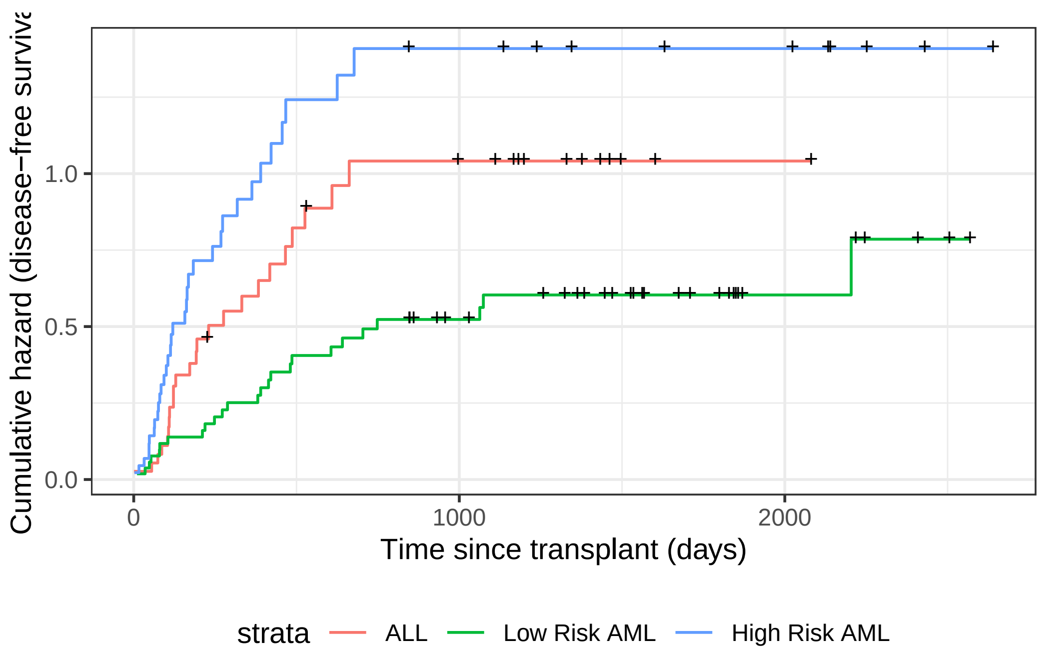


Figure 16: Disease-Free Cumulative Hazard by Disease Group

10 Nelson-Aalen Estimates of Cumulative Hazard and Survival

Definition 10.1 (Nelson-Aalen Cumulative Hazard Estimator)**.**
The point hazard at time t_i can be estimated by d_i/r_i, which leads to the **Nelson-Aalen estimator of the cumulative hazard**:

$$\hat{\Lambda}_{NA}(t) \stackrel{\text{def}}{=} \sum_{\{i:\ t_i \le t\}} \hat{\lambda}_i$$

Theorem 10.1 (Variance of Nelson-Aalen estimator)**.**
The variance of this estimator is approximately:

$$\begin{aligned} \hat{Var}\left(\hat{\Lambda}_{NA}(t)\right) &= \sum_{t_i \le t} \frac{(d_i/r_i)(1-d_i/r_i)}{r_i} \\ &\approx \sum_{t_i \le t} \frac{d_i}{r_i^2} \end{aligned} \tag{7}$$

Since $S(t) = \exp\{-\Lambda(t)\}$, the Nelson-Aalen cumulative hazard estimate can be converted into an alternate estimate of the survival function:

$$
\begin{aligned}
\hat{S}_{NA}(t) &= \exp\left\{-\hat{\Lambda}_{NA}(t)\right\} \\
&= \exp\left\{-\sum_{t_i \le t} \frac{d_i}{r_i}\right\} \\
&= \prod_{t_i \le t} \exp\left\{-\frac{d_i}{r_i}\right\} \\
&= \prod_{t_i \le t} \hat{\kappa}_i^{NA}
\end{aligned}
$$

where $\hat{\kappa}_i^{NA} = \exp\left\{-\hat{\lambda}_i\right\} = \exp\{-d_i/r_i\}$ is the Nelson-Aalen conditional survival factor (compare with the KM factor $\hat{\kappa}_i^{KM} = 1 - d_i/r_i$).

Compare these with the corresponding Kaplan-Meier estimates:

$$
\begin{aligned}
\hat{\Lambda}_{KM}(t) &= -\sum_{t_i \le t} \log\left\{1 - \frac{d_i}{r_i}\right\} \\
\hat{S}_{KM}(t) &= \prod_{t_i \le t} \left[1 - \frac{d_i}{r_i}\right]
\end{aligned}
$$

The product limit estimate and the Nelson-Aalen estimate often do not differ by much. The latter is considered more accurate in small samples and also directly estimates the cumulative hazard. The `"fleming-harrington"` method for `survfit()` reduces to Nelson-Aalen when the data are unweighted. We can also estimate the cumulative hazard as the negative log of the KM survival function estimate.

10.1 Application to `bmt` dataset

```
na_fit <- survfit(
  formula = surv ~ group,
  type = "fleming-harrington",
  data = bmt
)

km_fit <- survfit(
  formula = surv ~ group,
  type = "kaplan-meier",
  data = bmt
)

km_and_na <-
  bind_rows(
    .id = "model",
    "Kaplan-Meier" = km_fit |> fortify(surv.connect = TRUE),
    "Nelson-Aalen" = na_fit |> fortify(surv.connect = TRUE)
  ) |>
  as_tibble()
```

```
km_and_na |>
  ggplot(aes(x = time, y = surv, col = model)) +
  geom_step() +
  facet_grid(. ~ strata) +
  theme_bw() +
  ylab("S(t) = P(T>t)") +
```

```
  xlab("Survival time (t, days)") +
  theme(legend.position = "bottom")
```

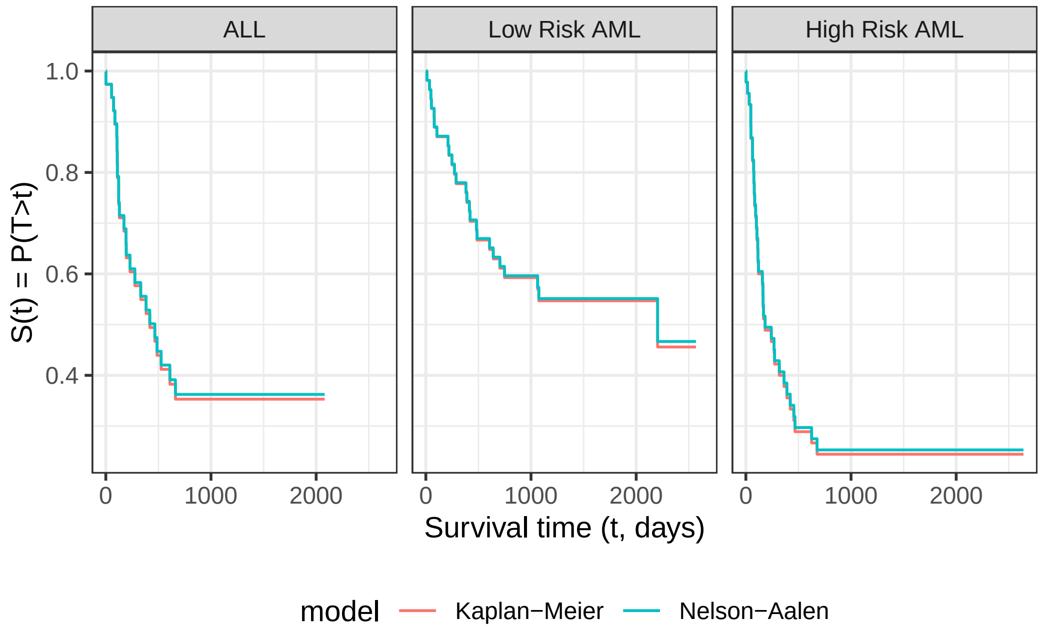


Figure 17: Kaplan-Meier and Nelson-Aalen Survival Function Estimates, stratified by disease group

The Kaplan-Meier and Nelson-Aalen survival estimates are very similar for this dataset.

Exercise 10.1. Compute the Nelson-Aalen (NA) estimated survival curve for the data in Table 3, by hand.

Solution

Solution 10.1. Let:

- n: total sample size
- y: study exit time;
- $d(y)$: number of events at y;
- $c(y)$: number exiting without events ("censored") at y
- $e(y) = d(y) + c(y)$: total exiting at y;
- $E(y)$: cumulative exits prior to y;
- $r(y) = n - E(y)$: number at risk at y;
- $r^*(y) = r(y) - e(y)$: number at risk after y;
- $\hat{\lambda}(y) = \frac{d(y)}{r(y)}$: Nelson-Aalen hazard increment;
- $\hat{\kappa}(y) = \exp\left\{-\hat{\lambda}(y)\right\}$: Nelson-Aalen conditional survival factor;
- $\hat{\Lambda}_{NA}(y) = \sum_{k:\, y_k \le y} \hat{\lambda}(y_k)$: Nelson-Aalen cumulative hazard estimate;
- $\hat{\mathrm{S}}_{NA}(y) = \exp\left\{-\hat{\Lambda}_{NA}(y)\right\} = \prod_{k:\, y_k \le y} \hat{\kappa}(y_k)$: Nelson-Aalen survival estimate.

```r
library(dplyr)
na_curve <-
  data1 |>
  summarise(.by  = Y,
            events = sum(D == 1),
            censored = sum(D == 0)) |>
  arrange(Y) |>
  mutate(
    study_size = nrow(data1),
    exiting = events + censored,
    exited = cumsum(exiting) |> dplyr::lag(default = 0),
    at_risk = study_size - exited,
    r_star = at_risk - exiting,
    hazard = events / at_risk,
    kappa = exp(-hazard),
    cusum_hazard = cumsum(hazard),
    na_surv_curve = exp(-cusum_hazard)
  ) |>
  select(-study_size)
na_curve |>
  mutate(
    hazard_math = paste0("\\frac{", events, "}{", at_risk, "}"),
    cusum_hazard_round = round(cusum_hazard, 4),
    na_surv_curve = paste0(
      "$\\expf{-", cusum_hazard_round, "}",
      " = ",
      round(na_surv_curve, 4),
      "$"
    ),
    cusum_hazard = paste0(
      "$",
      purrr::map_chr(
        row_number(),
        \(i) paste(hazard_math[seq_len(i)], collapse = " + ")
      ),
      " = ",
      cusum_hazard_round,
      "$"
    ),
    kappa = paste0(
      "$\\expf{-", hazard_math, "} = ",
      round(kappa, 4), "$"
    ),
    hazard = paste0(
      "$", hazard_math, " = ",
      round(hazard, 4), "$"
    )
  ) |>
  select(-hazard_math, -cusum_hazard_round) |>
  rename(
    `$y$`                                   = Y,
    `$d(y)$`                                = events,
    `$c(y)$`                                = censored,
    `$e(y)$`                                = exiting,
    `$E(y)$`                                = exited,
    `$r(y)$`                                = at_risk,
    `$r^*(y)$`                              = r_star,
    `$\\hat{\\haz}(y)$`                     = hazard,
    `$\\hat{\\cs}(y)$`                      = kappa,
    `$\\hat{\\cuhaz}_{NA}(y)$`              = cusum_hazard,
    `$\\hsurv_{NA}(y)$`                     = na_surv_curve
  ) |>
```

Table 7: Nelson-Aalen survival curve calculations

y	$d(y)$	$c(y)$	$e(y)$	$E(y)$	$r(y)$	$r^*(y)$	$\hat{\lambda}(y)$	$\hat{\kappa}(y)$	$\hat{\Lambda}_{NA}(y)$	$\hat{\text{S}}_{NA}(y)$
1	1	0	1	0	9	8	$\frac{1}{9} = 0.1111$	$\exp\{-\frac{1}{9}\} = 0.8948$	$\frac{1}{9} = 0.1111$	$\exp\{-0.1111\} = 0.8948$
3	1	0	1	1	8	7	$\frac{1}{8} = 0.125$	$\exp\{-\frac{1}{8}\} = 0.8825$	$\frac{1}{9} + \frac{1}{8} = 0.2361$	$\exp\{-0.2361\} = 0.7897$
7	1	0	1	2	7	6	$\frac{1}{7} = 0.1429$	$\exp\{-\frac{1}{7}\} = 0.8669$	$\frac{1}{9}+\frac{1}{8}+\frac{1}{7} = 0.379$	$\exp\{-0.379\} = 0.6846$
10	1	0	1	3	6	5	$\frac{1}{6} = 0.1667$	$\exp\{-\frac{1}{6}\} = 0.8465$	$\frac{1}{9}+\frac{1}{8}+\frac{1}{7}+\frac{1}{6} = 0.5456$	$\exp\{-0.5456\} = 0.5795$
13	0	1	1	4	5	4	$\frac{0}{5} = 0$	$\exp\{-\frac{0}{5}\} = 1$	$\frac{1}{9}+\frac{1}{8}+\frac{1}{7}+\frac{1}{6}+\frac{0}{5} = 0.5456$	$\exp\{-0.5456\} = 0.5795$
15	1	0	1	5	4	3	$\frac{1}{4} = 0.25$	$\exp\{-\frac{1}{4}\} = 0.7788$	$\frac{1}{9}+\frac{1}{8}+\frac{1}{7}+\frac{1}{6}+\frac{0}{5}+\frac{1}{4} = 0.7956$	$\exp\{-0.7956\} = 0.4513$
16	0	3	3	6	3	0	$\frac{0}{3} = 0$	$\exp\{-\frac{0}{3}\} = 1$	$\frac{1}{9}+\frac{1}{8}+\frac{1}{7}+\frac{1}{6}+\frac{0}{5}+\frac{1}{4}+\frac{0}{3} = 0.7956$	$\exp\{-0.7956\} = 0.4513$

Exercise 10.2. Implement the NA survival curve estimator in R. Check the output of your implementation against the version in the `survival` package.

Solution

Solution 10.2.

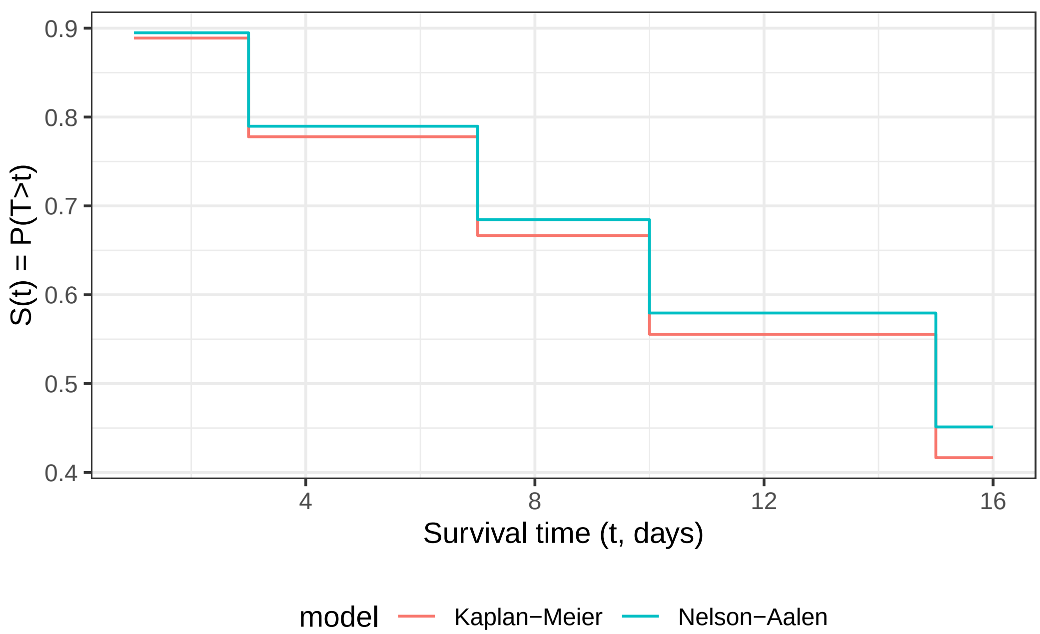
```
NA_model <-
  data1 |>
  survfit(formula = surv ~ 1,
          type = "fleming-harrington")

NA_model |> summary()
#> Call: survfit(formula = surv ~ 1, data = data1, type = "fleming-harrington")
#>
#>  time n.risk n.event survival std.err lower 95% CI upper 95% CI
#>     1      9       1    0.895  0.0994        0.720        1.000
#>     3      8       1    0.790  0.1321        0.569        1.000
#>     7      7       1    0.685  0.1506        0.445        1.000
#>    10      6       1    0.579  0.1599        0.337        0.995
#>    15      4       1    0.451  0.1680        0.218        0.936
```

Exercise 10.3. Add the NA estimated survival curve to the graph from Exercise 7.3.

Solution

Solution 10.3.

```
km_and_na <-
  bind_rows(
    .id = "model",
    "Kaplan-Meier" = KM_model |> fortify(surv.connect = FALSE),
    "Nelson-Aalen" = NA_model |> fortify(surv.connect = FALSE)
  ) |>
  as_tibble()

km_and_na |>
  ggplot(aes(x = time, y = surv, col = model)) +
  geom_step() +
  theme_bw() +
  ylab("S(t) = P(T>t)") +
  xlab("Survival time (t, days)") +
  theme(legend.position = "bottom")
```



Exercise 10.4. Find the NA estimate of median survival time.

Solution

Solution 10.4.

```
NA_model |> quantile(prob = 0.5) |> as_tibble()
#> # A tibble: 1 x 3
#>   quantile lower upper
#>      <dbl> <dbl> <dbl>
#> 1       15     7    NA
```

Exercise 10.5. Describe the similarities and differences between the graphs of the KM and NA survival function estimates.

Solution

Solution 10.5. The curves are very similar for this data set, with the KM curve returning slightly lower estimates of survival.

11 Empirical Inverse Survival Function

Definition 11.1 (Empirical inverse survival function)**.** Given a time-to-event dataset, the **empirical inverse survival function** (empirical ISF), also called the **empirical survival quantile function** (empirical SQF), $\hat{\mathrm{S}}^{-1}(p)$ replaces the population survival function $\mathrm{S}(t)$ with an estimated survival function $\hat{\mathrm{S}}(t)$:

$$\hat{\mathrm{S}}^{-1}(p) \stackrel{\text{def}}{=} \inf\Big\{t \geq 0 : \hat{\mathrm{S}}(t) \leq p\Big\}, \quad 0 < p < 1.$$

Since $\hat{\mathrm{S}}(t)$ is a non-increasing step function, $\hat{\mathrm{S}}^{-1}(p)$ equals the smallest observed event time at which the estimated survival probability has dropped to or below p.

From the Kaplan-Meier estimator. Substituting $\hat{\mathrm{S}}_{KM}(t)$ from Definition 7.2:

$$\hat{\mathrm{S}}^{-1}_{KM}(p) = \inf\left\{t \geq 0 : \prod_{t_i \leq t}\left[1 - \frac{d_i}{r_i}\right] \leq p\right\}.$$

From the Nelson-Aalen estimator. Substituting $\hat{\mathrm{S}}_{NA}(t) = \exp\Big\{-\hat{\Lambda}_{NA}(t)\Big\}$ from Definition 10.1:

$$\hat{\mathrm{S}}^{-1}_{NA}(p) = \inf\left\{t \geq 0 : \exp\left\{-\sum_{t_i \leq t}\frac{d_i}{r_i}\right\} \leq p\right\}.$$

In R, both estimators are computed from a `survfit()` object using `quantile()`.

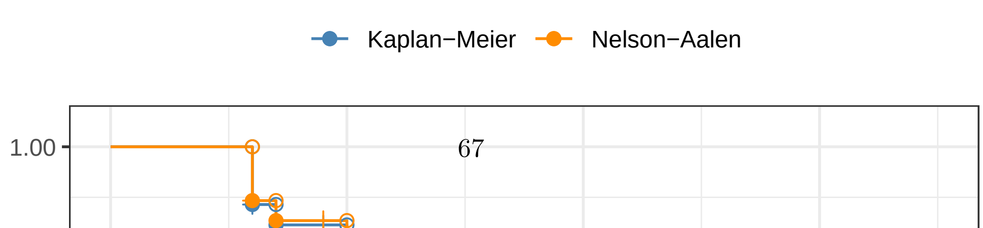
Exm

Example 11.1 (Empirical ISF for 6-MP patients)**.** Using the `drug6mp` dataset, we compute the empirical ISF for the 6-MP patients. The KM and Nelson-Aalen survival estimates at each event time are:

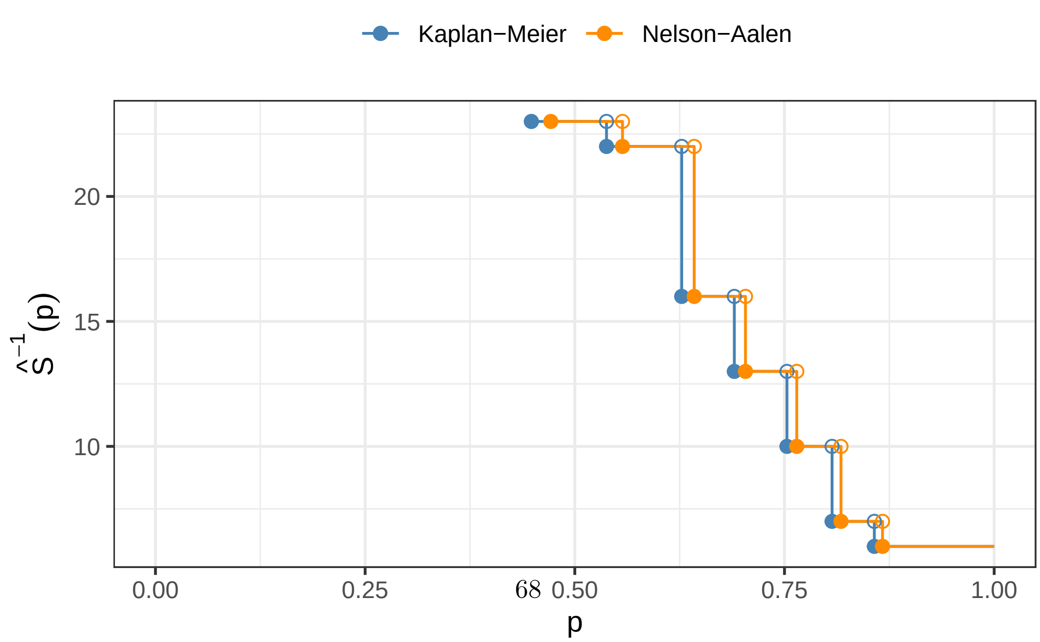
```r
library(KMsurv)
library(dplyr)
library(survival)
data(drug6mp)

km_fit <- drug6mp |>
  mutate(surv = Surv(t2, relapse)) |>
  survfit(formula = surv ~ 1, data = _)

na_fit <- drug6mp |>
  mutate(surv = Surv(t2, relapse)) |>
  survfit(formula = surv ~ 1, type = "fleming-harrington", data = _)

tbl <- tibble(
  time = km_fit$time,
  n.risk = km_fit$n.risk,
  n.event = km_fit$n.event,
  surv_km = km_fit$surv,
  surv_na = na_fit$surv
) |>
  filter(n.event > 0)

library(knitr)
kable(
  tbl,
  digits = 3,
  col.names = c(
    "Time (months)",
    "At risk $r_i$",
    "Events $d_i$",
    "$\\hat{S}_{KM}(t)$",
    "$\\hat{S}_{NA}(t)$"
  )
)
```

Time (months)	At risk r_i	Events d_i	$\hat{S}_{KM}(t)$	$\hat{S}_{NA}(t)$
6	21	3	0.857	0.867
7	17	1	0.807	0.817
10	15	1	0.753	0.765
13	12	1	0.690	0.704
16	11	1	0.627	0.642
22	7	1	0.538	0.557
23	6	1	0.448	0.471

```r
library(ggplot2)

surv_steps <- rbind(
  data.frame(
    time = c(0, km_fit$time), surv = c(1, km_fit$surv),
    estimator = "Kaplan-Meier"
  ),
  data.frame(
    time = c(0, na_fit$time), surv = c(1, na_fit$surv),
    estimator = "Nelson-Aalen"
  )
)

cens_marks <- rbind(
  data.frame(
    time = km_fit$time[km_fit$n.censor > 0],
    surv = km_fit$surv[km_fit$n.censor > 0],
    estimator = "Kaplan-Meier"
  ),
  data.frame(
    time = na_fit$time[na_fit$n.censor > 0],
    surv = na_fit$surv[na_fit$n.censor > 0],
    estimator = "Nelson-Aalen"
  )
)

ev_idx_km <- km_fit$n.event > 0
s_after_km <- km_fit$surv[ev_idx_km]
s_before_km <- c(1, head(s_after_km, -1))
ev_idx_na <- na_fit$n.event > 0
s_after_na <- na_fit$surv[ev_idx_na]
s_before_na <- c(1, head(s_after_na, -1))

open_surv <- rbind(
  data.frame(time = km_fit$time[ev_idx_km], surv = s_before_km, estimator = "Kaplan-Meier"),
  data.frame(time = na_fit$time[ev_idx_na], surv = s_before_na, estimator = "Nelson-Aalen")
)
closed_surv <- rbind(
  data.frame(time = km_fit$time[ev_idx_km], surv = s_after_km, estimator = "Kaplan-Meier"),
  data.frame(time = na_fit$time[ev_idx_na], surv = s_after_na, estimator = "Nelson-Aalen")
)

ggplot(surv_steps, aes(x = time, y = surv, color = estimator)) +
  geom_step() +
  geom_point(data = cens_marks, shape = 3, size = 2, show.legend = FALSE) +
  geom_point(data = open_surv, shape = 1, size = 2) +
  geom_point(data = closed_surv, shape = 19, size = 2) +
  scale_color_manual(
    values = c("Kaplan-Meier" = "steelblue", "Nelson-Aalen" = "darkorange")
  ) +
  coord_cartesian(ylim = c(0, 1.05)) +
  labs(x = "Time (months)", y = expression(hat(S)(t)), color = NULL) +
  theme_bw() +
  theme(legend.position = "top")
```



```r
ev_km <- km_fit$n.event > 0
t_ev_km <- km_fit$time[ev_km]
s_ev_km <- km_fit$surv[ev_km]

ev_na <- na_fit$n.event > 0
t_ev_na <- na_fit$time[ev_na]
s_ev_na <- na_fit$surv[ev_na]

isf_steps <- rbind(
  data.frame(
    p = c(1, s_ev_km), t = c(t_ev_km[1], t_ev_km),
    estimator = "Kaplan-Meier"
  ),
  data.frame(
    p = c(1, s_ev_na), t = c(t_ev_na[1], t_ev_na),
    estimator = "Nelson-Aalen"
  )
)
isf_steps <- isf_steps[order(isf_steps$estimator, isf_steps$p), ]

open_isf <- rbind(
  data.frame(p = head(s_ev_km, -1), t = tail(t_ev_km, -1), estimator = "Kaplan-Meier"),
  data.frame(p = head(s_ev_na, -1), t = tail(t_ev_na, -1), estimator = "Nelson-Aalen")
)
closed_isf <- rbind(
  data.frame(p = s_ev_km, t = t_ev_km, estimator = "Kaplan-Meier"),
  data.frame(p = s_ev_na, t = t_ev_na, estimator = "Nelson-Aalen")
)

ggplot(isf_steps, aes(x = p, y = t, color = estimator)) +
  geom_step() +
  geom_point(data = open_isf, shape = 1, size = 2) +
  geom_point(data = closed_isf, shape = 19, size = 2) +
  scale_color_manual(
    values = c("Kaplan-Meier" = "steelblue", "Nelson-Aalen" = "darkorange")
  ) +
  coord_cartesian(xlim = c(0, 1)) +
  labs(x = "p", y = expression(hat(S)^{-1}*(p)), color = NULL) +
  theme_bw() +
  theme(legend.position = "top")
```



The rightmost step is drawn out to $p = 1$ for visual continuity only. The inverse survival function is defined for $0 < p < 1$; at the boundary, $\hat{\mathrm{S}}^{-1}(1) = \inf\left\{t \geq 0 : \hat{\mathrm{S}}(t) \leq 1\right\} = 0$, since $\hat{\mathrm{S}}(0) = 1$.
The empirical median survival time is the smallest event time t at which the estimated survival probability falls to or below 0.5.
From the table:

- $\hat{\mathrm{S}}_{KM}(22) \approx 0.538 > 0.5$ and $\hat{\mathrm{S}}_{KM}(23) \approx 0.448 \leq 0.5$, so $\hat{\mathrm{S}}_{KM}^{-1}(0.5) = 23$ months.
- $\hat{\mathrm{S}}_{NA}(22) \approx 0.557 > 0.5$ and $\hat{\mathrm{S}}_{NA}(23) \approx 0.471 \leq 0.5$, so $\hat{\mathrm{S}}_{NA}^{-1}(0.5) = 23$ months.

In R:

```r
quantile(km_fit, probs = 0.5)
#> $quantile
#> 50
#> 23
#>
#> $lower
#> 50
#> 16
#>
#> $upper
#> 50
#> NA
```

```r
quantile(na_fit, probs = 0.5)
#> $quantile
#> 50
#> 23
#>
#> $lower
#> 50
#> 16
#>
#> $upper
#> 50
#> NA
```

Both the KM and Nelson-Aalen estimators give an estimated median relapse-free survival time of **23 months** for the 6-MP patients.

12 Interval Censoring

This section is adapted from (Vittinghoff et al. 2012, chap. 6).

Standard survival analysis assumes that the time of events occurring during the study is known more or less exactly. This is almost always the case for well-documented events like:

- Death
- Hospitalization
- Diagnosis of AIDS

However, the timing of many events is not observed with this level of precision.

12.1 What is Interval Censoring?

Definition 12.1 (Interval Censoring)**. Interval censoring** occurs when the exact time of an event is not known, but we know it occurred within a specific time interval.

12.2 Common Examples

1. **HIV infection in prospective cohort studies**: Participants are tested for infection at semi-annual visits. The actual time of infection is only known to fall between the last negative test and the first positive test.
2. **Development of cervical abnormalities**: Clinical exams may be performed periodically, months or years apart. Newly observed changes may have occurred at any time since the last exam.

12.3 Approaches to Interval Censoring

When intervals are regularly spaced:

- Pooled logistic regression (Vittinghoff et al. 2012, sec. 5.5.2) can handle interval censoring when intervals arise from a regular study follow-up schedule

When intervals are irregular:

- Unequal spacing between intervals
- Intervals that vary by individual
- Requires specialized methods beyond the scope of these notes

12.4 Numerical Example: MIRA HSV-2 Study

The `mira_hsv` dataset from the `rmb` package contains data from the MIRA randomized trial evaluating HIV prevention (Bruyn et al. 2011). Participants were tested for HSV-2 antibodies every 3 months.

The data have a **panel structure**: one row per participant per visit, with the HSV-2 test result at each visit.

```r
library(rmb)

# Show panel data for three example participants
example_ids <- c(28, 103, 119)

mira_hsv_example <- mira_hsv[
  mira_hsv$id %in% example_ids,
  c("id", "mos", "hsv2")
]

knitr::kable(
  mira_hsv_example,
  col.names = c("Subject ID", "Months", "HSV-2 positive")
)
```

Table 8: HSV-2 test results for three example participants in the MIRA study. For subjects 28 and 103, the seroconversion time is known only to fall in the interval (15, 18] months. For subject 119, seroconversion occurred in (9, 12] months.

Subject ID	Months	HSV-2 positive
28	3	0
28	6	0
28	9	0
28	12	0
28	15	0
28	18	1
103	3	0
103	6	0
103	9	0

Table 8: HSV-2 test results for three example participants in the MIRA study. For subjects 28 and 103, the seroconversion time is known only to fall in the interval (15, 18] months. For subject 119, seroconversion occurred in (9, 12] months.

Subject ID	Months	HSV-2 positive
103	12	0
103	15	0
103	18	1
119	3	0
119	6	0
119	9	0
119	12	1

For participants who seroconverted, the exact time of infection is unknown, but bounded by the last negative and first positive test. This is the defining feature of interval censoring.

The interval-censored structure for these three participants is:

Subject	Last negative visit (months)	First positive visit (months)	Interval
28	15	18	(15, 18]
103	15	18	(15, 18]
119	9	12	(9, 12]

Since visits occur every 3 months, the infection time is known to within a 3-month window. This regular spacing allows pooled logistic regression to handle the interval censoring, as described in (Vittinghoff et al. 2012, sec. 5.5.2).

13 Left-Truncation

This section is adapted from (Vittinghoff et al. 2012, chap. 6).

13.1 Choosing the Time Origin

Survival times are measured from some initial time, with more than one possible choice of origin.

Exm

Example 13.1 (Time origin choice in the PBC study)**.** In the Dickson et al. (1989) Primary Biliary Cholangitis (PBC) study, survival time could be measured from:

- **Cohort enrollment**: time from when the patient entered the study
- **Diagnosis**: time from PBC diagnosis (more biologically meaningful)

When using time-since-diagnosis as the timescale, patients who had already survived some time since diagnosis before enrolling introduce **left-truncation**.

13.2 What is Left-Truncation?

Left-truncation occurs when some survival times are not observed because the sampling scheme tends to miss short survival times.

Definition 13.1 (Left-Truncation)**. Left-truncated** data arise when individuals can only enter the study if they survive beyond a certain time point. Those who experience the event before that time point are never observed.

Key feature: There must be a time delay between:

1. The event that defines the time origin (e.g., diagnosis)
2. Entry into the study cohort (e.g., enrollment)

13.3 Left-Truncation vs. Staggered Entry

Important distinction:

- **Staggered entry**: Participants enroll at different calendar times
  - Does NOT necessarily imply left-truncation
  - Example: enrolling patients at the time of diagnosis (truncation times = 0)
- **Left-truncation**: Participants must survive some period before they can be enrolled
  - Example: recruiting from a referral center where months/years elapse between diagnosis and enrollment

13.4 Why Left-Truncation Matters

Patients with rapid disease progression are less likely to be enrolled because they may:

- Die before referral to the study center
- Die before recruitment into the study

This leads to:

- **Undercounting** of short survival times
- **Selection bias** toward longer survivors
- **Overestimation** of survival probabilities if ignored

13.5 Truncated vs. Censored Data

Censored data:

- Event time falls outside the follow-up period
- Data are **incomplete** but the individual is observed

Truncated data:

- Individual is not observed at all if they would have had an event outside the observation window
- Truncated individuals leave no trace
  - Called "ghosts" in the survival analysis literature

13.6 Independent Truncation Assumption

Analysis under left-truncation requires the **independent truncation assumption**:

The time of delayed entry and subsequent survival are independent.

This is satisfied when:

- Disease incidence and post-diagnosis survival are independent

13.7 Implementation

Denote:

- V: truncation time (delay between origin and study entry)
- X: follow-up time relative to the time origin
- δ: censoring indicator

In R:

Use the `Surv()` function with entry time:

```
Surv(time  = entry_time,
     time2 = exit_time,
     event = status)
```

In Stata:

```
stset years_since_diag, failure(status) entry(disease_dur)
```

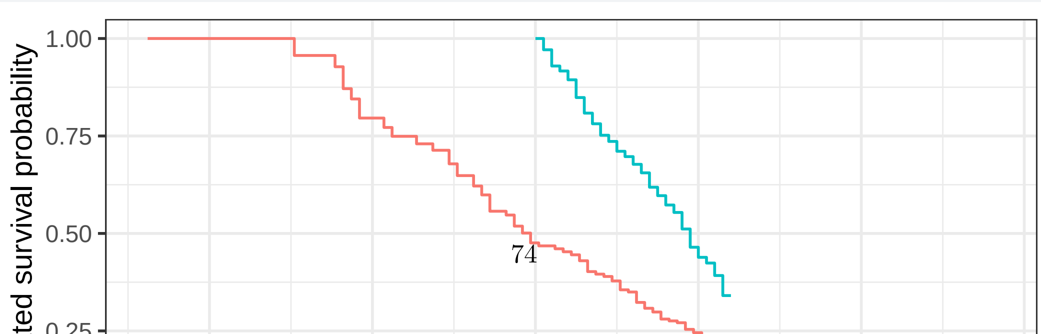
13.8 Numerical Example: PBC Study

The `pbc` dataset from the `rmb` package contains data from a clinical trial of D-penicillamine treatment in primary biliary cholangitis (PBC) (Dickson et al. 1989).

Here we demonstrate the effect of left-truncation by comparing analyses using two different time scales:

1. Time from enrollment (standard approach, no truncation)
2. Age as the time scale (introduces left-truncation, since patients are observed from their current age, not from birth)

```r
library(rmb)
library(survival)
library(ggplot2)
library(dplyr)

pbc_data <- rmb::pbc

# Analysis 1: time from enrollment (no truncation)
km_enroll <- survfit(
  Surv(years, as.numeric(status) == 1) ~ 1,
  data = pbc_data
)

# Analysis 2: age as time scale (left-truncated)
km_age <- survfit(
  Surv(time = age, time2 = age + years, event = as.numeric(status) == 1) ~ 1,
  data = pbc_data
)

# Extract KM estimates at specific times for each analysis
km1_summary <- summary(km_enroll, times = seq(0, 12, by = 0.5))
km2_summary <- summary(km_age, times = seq(26, 78, by = 0.5))

km1_df <- tibble(
  time = km1_summary$time,
  surv = km1_summary$surv,
  analysis = "Time from enrollment"
)

km2_df <- tibble(
  time = km2_summary$time - median(pbc_data$age),
  surv = km2_summary$surv,
  analysis = paste0(
    "Age as time scale\n",
    "(left-truncated; centered at median enrollment age)"
  )
)

km_combined <- bind_rows(km1_df, km2_df)

ggplot(km_combined) +
  aes(x = time, y = surv, color = analysis) +
  geom_step() +
  labs(
    x = "Time (years)",
    y = "Estimated survival probability",
    color = "Analysis",
    caption = "Data: rmb::pbc (PBC clinical trial, Dickson et al. 1989)"
  ) +
  scale_y_continuous(limits = c(0, 1)) +
  theme_bw() +
  theme(legend.position = "bottom")
```



The curve using age as the time scale accounts for the fact that participants were only observed from their age at enrollment. When centered at the median enrollment age, the two analyses can be compared on a common scale. Note that ignoring this truncation would lead to overestimated survival: participants who died at younger ages — before reaching their enrollment age — were never observed and are excluded from the data, leading to a risk set that over-represents longer survivors.

13.9 Effect of Ignoring Left-Truncation

When left-truncation is ignored:

- Survival probabilities are **overestimated** (especially at early time points)
- The analysis fails to account for undersampling of short survival times
- Hazard ratios in Cox models may be attenuated (effect is less predictable)

The following example illustrates the bias using the PBC data. The naive analysis treats all participants as entering the risk set at the earliest observed age, whereas the proper analysis uses counting-process notation to enter each participant at their actual enrollment age.

```
km_naive_age <- survfit(
  Surv(age + years, as.numeric(status) == 1) ~ 1,
  data = pbc_data
)

# Extract estimates at age 60 for comparison
surv_naive_at_sixty  <- summary(km_naive_age, times = 60)$surv
surv_proper_at_sixty <- summary(km_age, times = 60)$surv
```

At age 60, the naive analysis (ignoring delayed entry) estimates survival at 64.8%, compared to 22.3% with the proper left-truncation correction.

The naive estimate is inflated because the risk set at each age incorrectly includes participants who had not yet been enrolled (and thus had not actually been observed to be at risk).

13.10 Right-Truncation

Right-truncation can also occur if:

- Study recruits based on an endpoint
- People with large event times (or who never had the event) are not recruited

Example: A fecundability study that excludes couples who never conceive exhibits right-truncation.

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