STAT 6390: Analysis of Survival Data

Textbook coverage: Chapter 2

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Survival, hazard and cumulative hazard functions

- Define T as the random variable of the actual (uncensored, untruncated) survival time of an individual.
- We assume the support of T is non-negative or $(0, \infty)$.
- We call T the *random variable* associated with the survival time, and we define T has a cumulative distribution function given by $F(t) = \mathrm{P}(T \leq t)$.
- The survival function of T is then defined as

$$S(t) = 1 - \mathrm{P}(T \leq t) = 1 - F(t).$$

- Why are we more interested in $S(t)$?

Survival, hazard and cumulative hazard functions

- The *hazard function* is widely used to survival analysis.
- The hazard function $h(t)$ is defined below

$$h(t) = \lim_{\mathrm{d}t \to 0} \frac{\mathrm{P}(t \leq T < t + \mathrm{d}t | T \geq t)}{\mathrm{d}t}. \tag{1}$$

- $\mathrm{P}(t \leq T < t + \mathrm{d}t | T \geq t)$ is a conditional probability.
- The conditional probability is then expressed as a probability per unit time by dividing by the time interval, $\mathrm{d}t$, to give a *rate*.
- The function $h(t)$ is also referred to as the *hazard rate*, the *instantaneous death rate*, the *intensity rate*, or the *force of mortality*.
- Event rate at time t, conditional on the event not having occurred before t.

Survival, hazard and cumulative hazard functions

- In terms of probability, if t is measured in days, $h(t)$ is the approximate probability that an individual, who is *at risk of the event* occurring at the start of day t, experiences the event during that day.
  - In this case $\mathrm{d}t = 1$.
  - $\lim_{\mathrm{d}t \to 0}$ can be thought of as changing the unit from days to hours, minutes, seconds, milliseconds...
- If the event of interest is not death, $h(t)$ can also be regarded as the *expected number of events* experienced by an individual in unit time, given that the event has not occurred before then.
  - Think of $\mathrm{E}\{\mathrm{I}(\cdot)\} = \mathrm{P}(\cdot)$.
  - The part "given that the event..." might be ignored if events follow the Poisson process.

Survival, hazard and cumulative hazard functions

- The definition in (1) leads to some useful relationships between survival and hazard functions:

$$(1) = \lim_{\mathrm{d}t \to 0} \frac{\mathrm{P}(t \le T < t + \mathrm{d}t)}{\mathrm{d}t \cdot \mathrm{P}(T \ge t)} = \lim_{\mathrm{d}t \to 0} \frac{F(t + \mathrm{d}t) - F(t)}{\mathrm{d}t} \cdot \frac{1}{\mathrm{P}(T \ge t)} = \frac{\mathrm{d}F(t)}{\mathrm{d}t} \cdot \frac{1}{S(t)}.$$

- $h(t)$ is approximately the probability that an individual experiences an event at this instant (t) given that he/she is risk free up to t.
- If T is a continuous random variable, then we have

$$h(t) = \frac{f(t)}{S(t)}. \tag{2}$$

- This shows that from any one of the three functions, $f(t)$, $S(t)$, and $h(t)$, the other two can be determined.

Survival, hazard and cumulative hazard functions

- Equation (2) also implies

$$h(t) = -\frac{\mathrm{d}}{\mathrm{d}t}\{\log S(t)\} \text{ and } S(t) = e^{-H(t)},$$

  where $H(t) = \int_0^t h(u)\,\mathrm{d}u$ is the *cumulative hazard function*.
- Similarly, the cumulative hazard function can also be obtained from

$$H(t) = -\log S(t).$$

- The cumulative hazard function is the cumulative risk of an event occurring by time t.
- If the event is death, then $H(t)$ summarizes the risk of death up to time t, given that death has not occurred by t.
- If the event is not death, $H(t)$ can be interpreted as the expected number of events that occur in the interval $(0, t)$.

Survival, hazard and cumulative hazard functions

- It is possible for $H(t) > 1$, $h(t) > 1$, or $f(t) > 1$.
- $F(t)$, $S(t)$ are bounded in $[0, 1]$.
- $F(t)$ and $H(t)$ are non-decreasing; $S(t)$ is non-increasing.
- $h(t)$ can go up and down.
- For example, suppose $T \sim \exp(\lambda)$, where λ is the rate. Then
  - $S(t) = e^{-\lambda t}$.
  - $h(t) = \lambda$.
  - $H(t) = \lambda t$.

Empirical survival function

- The $S(t)$ can be estimated non-parametrically with the *product limit* estimator, which is also known as the *Kaplan-Meier* estimator.
- We first assume none of survival times are censored.
- In this case, the survival probability at t, $S(t)$, is defined as

$$\hat{S}_e(t) = \frac{\#\text{ individuals with survival times} \geq t}{\#\text{ individuals in the data set}}. \tag{3}$$

- Equation (3) is called *empirical survival function*.
- Similarly, $\hat{F}_e(t) = 1 - \hat{S}_e(t)$ is called the *empirical cumulative distribution function*.

Empirical survival function

- We illustrate with the first 10 uncensored subjects in the `whas100` data.
- Make sure **`tidyverse`** package and `whas100` are properly loaded*.

```
> whas10 <- whas100 %>% filter(fstat > 0) %>% filter(row_number() <= 10)
> whas10
# A tibble: 10 x 9
      id admitdate  foldate      los lenfol fstat   age gender   bmi
   <int> <fct>      <fct>      <int>  <int> <int> <int>  <int> <dbl>
 1     1 3/13/1995  3/19/1995      4      6     1    65      0  31.4
 2     2 1/14/1995  1/23/1996      5    374     1    88      1  22.7
 3     3 2/17/1995  10/4/2001      5   2421     1    77      0  27.9
 4     4 4/7/1995   7/14/1995      9     98     1    81      1  21.5
 5     5 2/9/1995   5/29/1998      4   1205     1    78      0  30.7
 6     6 1/16/1995  9/11/2000      7   2065     1    82      1  26.5
 7     7 1/17/1995  10/15/1997     3   1002     1    66      1  35.7
 8     8 11/15/1994 11/24/2000    56   2201     1    81      1  28.3
 9     9 8/18/1995  2/23/1996      5    189     1    76      0  27.1
10    12 5/26/1995  9/29/1996     11    492     1    83      0  24.7
```

* see note 1 for details.

Empirical survival function

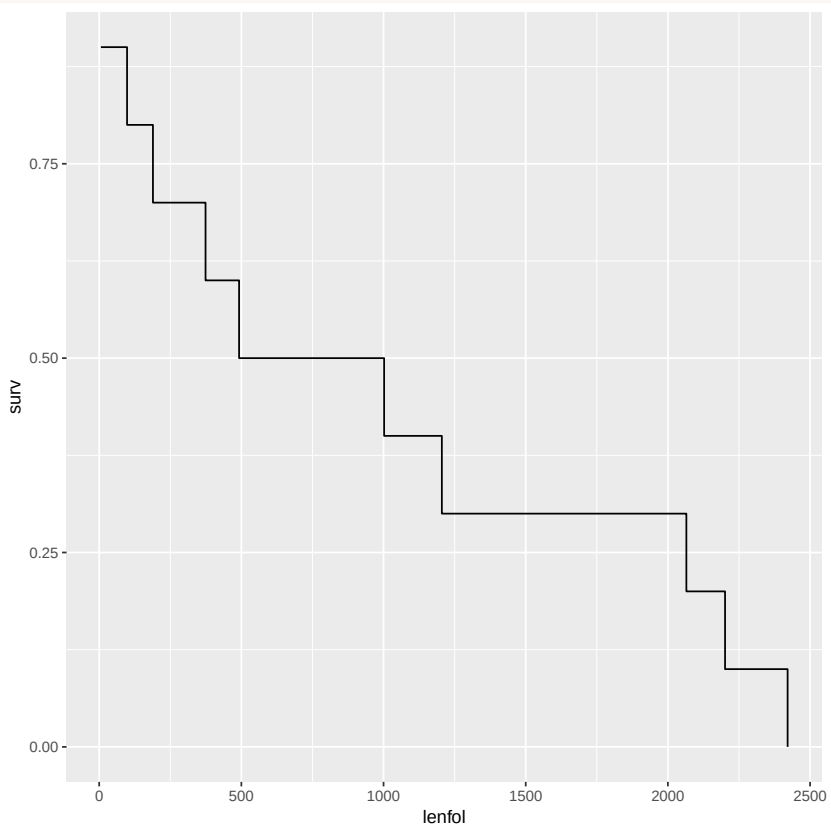
- The empirical estimates can be easily computed with `ecdf`.

```
> whas10 <- whas10 %>% mutate(surv = 1 - ecdf(lenfol)(lenfol))
> whas10
# A tibble: 10 x 10
      id admitdate  foldate      los lenfol fstat   age gender   bmi  surv
   <int> <fct>      <fct>      <int>  <int> <int> <int>  <int> <dbl> <dbl>
 1     1 3/13/1995  3/19/1995      4      6     1    65      0  31.4 0.9
 2     2 1/14/1995  1/23/1996      5    374     1    88      1  22.7 0.6
 3     3 2/17/1995  10/4/2001      5   2421     1    77      0  27.9 0
 4     4 4/7/1995   7/14/1995      9     98     1    81      1  21.5 0.8
 5     5 2/9/1995   5/29/1998      4   1205     1    78      0  30.7 0.3
 6     6 1/16/1995  9/11/2000      7   2065     1    82      1  26.5 0.200
 7     7 1/17/1995  10/15/1997     3   1002     1    66      1  35.7 0.4
 8     8 11/15/1994 11/24/2000    56   2201     1    81      1  28.3 0.100
 9     9 8/18/1995  2/23/1996      5    189     1    76      0  27.1 0.7
10    12 5/26/1995  9/29/1996     11    492     1    83      0  24.7 0.5
```

Empirical survival function

- The empirical survival function is a non-increasing step function.

```
> whas10 %>% ggplot(aes(lenfol, surv)) + geom_step(size = 1.2)
```

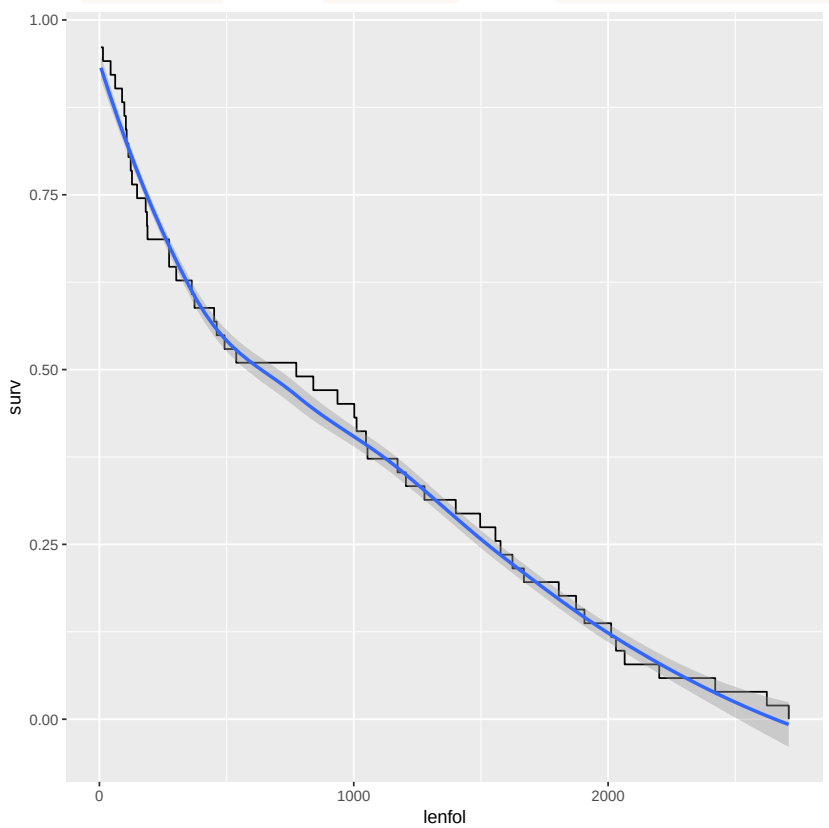


- The $\hat{S}_e(t)$ is 1 at $t = 0$ and 0 at the final death time.
- The $\hat{S}_e(t)$ is assumed to be constant between adjacent death times.

Empirical survival function

- Putting everything together, we could plot the empirical survival curve for all the uncensored subjects in `whas100`:

```
> whas100 %>% filter(fstat > 0) %>% mutate(surv = 1 - ecdf(lenfol)(lenfol)) %>%
+     ggplot(aes(lenfol, surv)) + geom_step() + geom_smooth()
```



- The pipeline between `ggplot` is "+" instead of "%>%".

Kaplan-Meier estiamtor

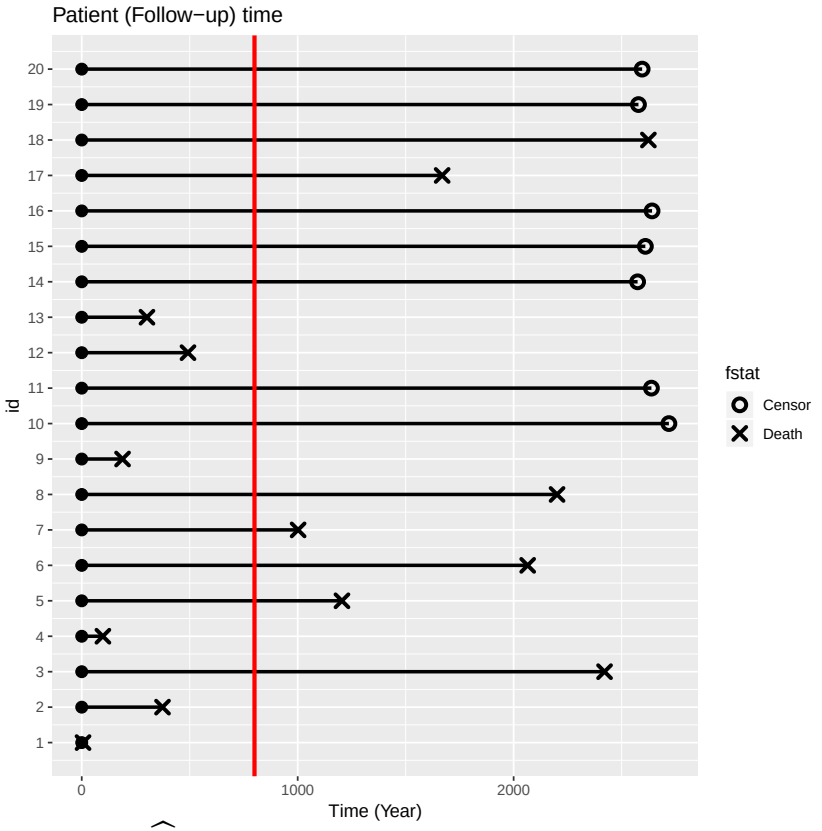
- With censoring, the same idea can be applied with proper adjustment.
- Kaplan-Meier estimator is the default estimator used by many packages.
- The basic idea is to decompose $\mathrm{P}(T > t)$ by conditioning on prior times.
- Suppose a sample size of n, $\mathrm{P}(T > t)$ can be decomposed as

$$\widehat{S}_{KM}(t) \doteq \mathrm{P}(T > t) = \mathrm{P}(T > t_{(0)}) \cdot \mathrm{P}(T > t_{(1)} | T > t_{(0)}) \cdot \mathrm{P}(T > t_{(2)} | T > t_{(1)}) \cdot \ldots \cdot \mathrm{P}(T > t | T > t_{(i)}),$$

  for a series of time intervals $0 \doteq t_{(0)} < t_{(1)} < \ldots < t_{(i)} < t$ for some $i \leq n$.
- In general, the series $\{t_{(1)}, \ldots, t_{(m)}\}$ denotes the m ordered death times.

Kaplan-Meier estiamtor

Suppose we want $\mathrm{P}(T > 800)$ among the first 20 patients in `whas1000`.



- There are 6 events before $t = 800$.
- The events occured at

$t_{(0)}$	$t_{(1)}$	$t_{(2)}$	$t_{(3)}$	$t_{(4)}$	$t_{(5)}$	$t_{(6)}$
0	6	98	189	302	374	492

$$\begin{aligned}\widehat{S}_{KM}(800) &= \mathrm{P}(T > 800) = \\ &= \mathrm{P}(T > 0) \times \mathrm{P}(T > 6 | T > 0) \times \mathrm{P}(T > 98 | T > 6) \times \ldots \times \mathrm{P}(T > 492 | T > 374) \\ &= 1 \times \frac{19}{20} \times \frac{18}{19} \times \frac{17}{18} \times \frac{16}{17} \times \frac{15}{16} \times \frac{14}{15} = \frac{14}{20} = 70\%\end{aligned}$$

$\widehat{S}_{KM}(800) = \hat{S}_e(800)$ here, why?

Kaplan-Meier estimator

- The Kaplan-Meier estimator can be obtained with the `survfit` function.

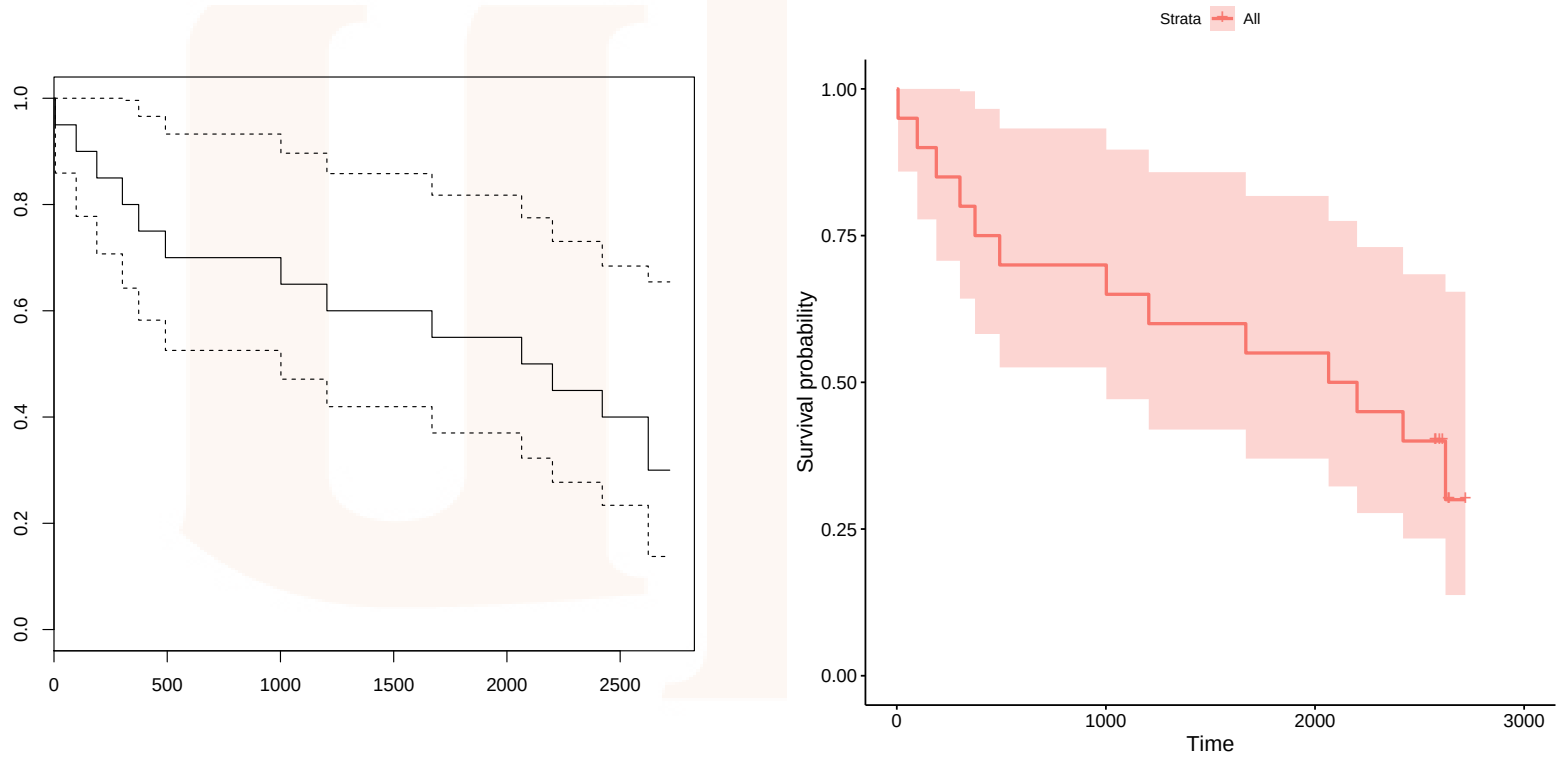
```
> library(survival)
> km <- survfit(Surv(lenfol, fstat) ~ 1, data = whas100, subset = id <= 20)
> summary(km)
Call: survfit(formula = Surv(lenfol, fstat) ~ 1, data = whas100, subset = id <=
    20)

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
    6     20       1     0.95  0.0487        0.859        1.000
   98     19       1     0.90  0.0671        0.778        1.000
  189     18       1     0.85  0.0798        0.707        1.000
  302     17       1     0.80  0.0894        0.643        0.996
  374     16       1     0.75  0.0968        0.582        0.966
  492     15       1     0.70  0.1025        0.525        0.933
 1002     14       1     0.65  0.1067        0.471        0.897
 1205     13       1     0.60  0.1095        0.420        0.858
 1669     12       1     0.55  0.1112        0.370        0.818
 2065     11       1     0.50  0.1118        0.323        0.775
 2201     10       1     0.45  0.1112        0.277        0.731
 2421      9       1     0.40  0.1095        0.234        0.684
 2624      4       1     0.30  0.1194        0.138        0.654
```

Kaplan-Meier estimator

- The Kaplan-Meier curve can be plotted with `plot` or `ggsurvplot`.

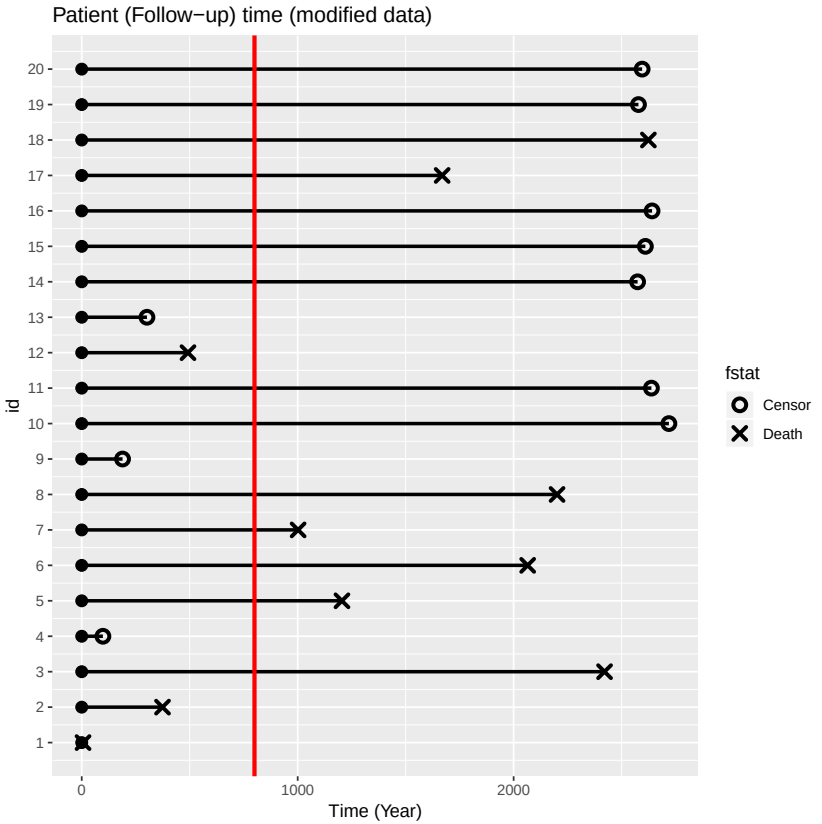
```
> library(survminer)
> plot(km)
> ggsurvplot(km)
```



- Since **`survminer`** depends on the newest version of **`survMisc`**, you might need to update the latter to be able to use `ggsurvplot`.

Kaplan-Meier estimator

Suppose we want $\mathrm{P}(T > 800)$ based on the following modified data:



- There are 3 events before $t = 800$.
- The events occured at

$t_{(0)}$	$t_{(1)}$	$t_{(2)}$	$t_{(3)}$
0	6	374	492

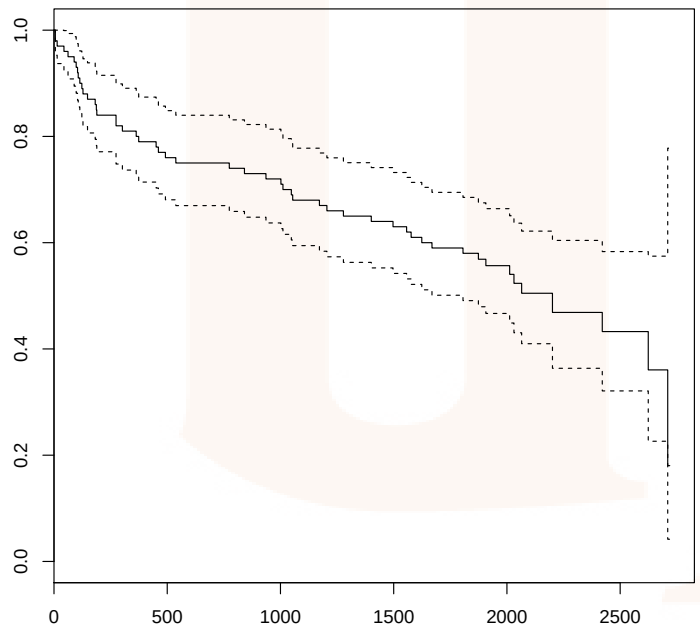
- In this modified data, $t = 98, 189, 302$ are considered as censored.

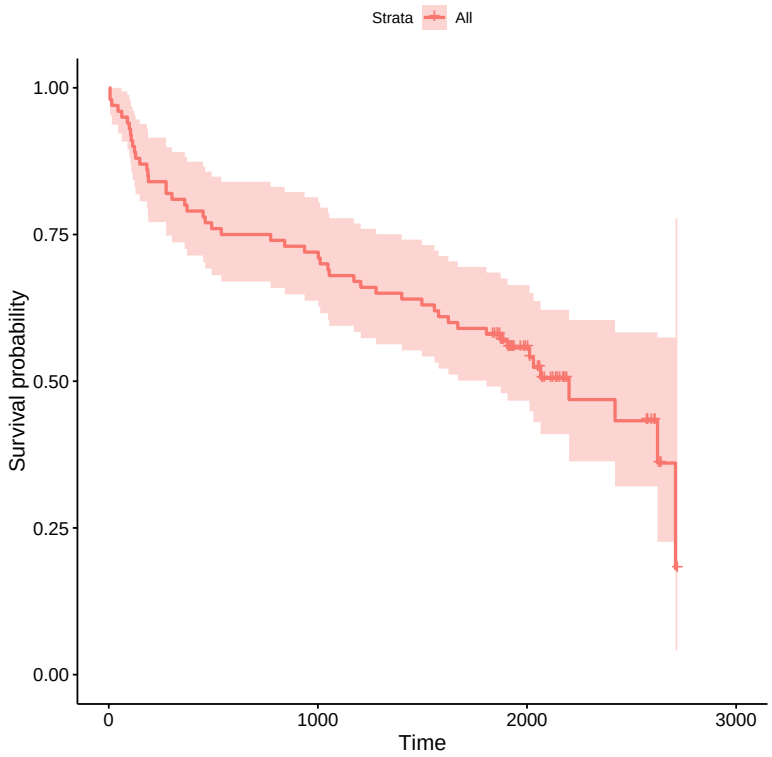
$$\begin{aligned}\widehat{S}_{KM}(800) &= \mathrm{P}(T > 800) = \\ &= \mathrm{P}(T > 0) \times \mathrm{P}(T > 6 | T > 0) \times \mathrm{P}(T > 374 | T > 6) \times \mathrm{P}(T > 492 | T > 374) \\ &= 1 \times \frac{19}{20} \times \frac{15}{16} \times \frac{14}{15} \approx 83.1\%\end{aligned}$$

Kaplan-Meier estimator

- The Kaplan-Meier estimator for the whole data is

```
> library(survival)
> km <- survfit(Surv(lenfol, fstat) ~ 1, data = whas100)
> plot(km)
> ggsurvplot(km)
```





- If the last observed time corresponds to a censored observation, then the estimate of the survival function does not go to zero.

Kaplan-Meier estimator

- Suppose we have a sample of n independent observations $(t_i, c_i), i = 1, 2, \ldots, n$.
- Suppose there are m deaths and $m \leq n$.
- The series $\{t_{(1)}, \ldots, t_{(m)}\}$ are the m ordered death times.
- The Kaplan-Meier estimator has the form

$$\widehat{S}_{KM}(t) = \prod_{t_{(i)} \leq t} \frac{n_i - d_i}{n_i} = \prod_{t_{(i)} \leq t} 1 - \frac{d_i}{n_i},$$

  where n_i is the number of individual who are alive at $t_{(i)}$ (at risk), and d_i is the number of individual who died at $t_{(i)}$.
- A potential problem with the Kaplan-Meier estimator is when n_i is small and $n_i = d_i$ occurs at early time.

Nelson-Aalon estimator

- An alternative estimate of $\widehat{S}_{KM}(t)$ is the *Nelson-Aalon estimator*:

$$\widehat{S}_{NA}(t) = \prod_{t_{(i)} \le t} \exp\left(-\frac{d_i}{n_i}\right).$$

- The main idea is to see d_i/n_i as the event rate, i.e., $h(t_{(i)}) = d_i/n_i$.
- Recall the relationship $h(t) = f(t)/S(t)$ and think of d_i/n and n_i/n are raw estimates of $f(t)$ and $S(t)$.
- By the similar argument, we have

$$\widehat{H}_{NA}(t) \doteq H(t) = \sum_{t_{(i)} \le t} d_i/n_i, \text{ and } S(t) = e^{-\widehat{H}_{NA}(t)} = \widehat{S}_{NA}(t).$$

- $\widehat{S}_{NA}(t)$ and $\widehat{S}_{KM}(t)$ are derived differently, but both based on d_i and n_i.
- In general $\widehat{S}_{NA}(t) \ge \widehat{S}_{KM}(t)$ but $\widehat{S}_{NA}(t) \approx \widehat{S}_{KM}(t)$.

Nelson-Aalon estimator

- $\widehat{S}_{NA}(t)$ has slightly nicer properties and is more stable.
- If the interest is in estimating the cumulative hazard function, $H(t)$, we can use either the $\widehat{H}_{NA}(t)$, or $\widehat{H}_{KM}(t) = -\log \widehat{S}_{KM}(t)$.
- The $\widehat{H}_{KM}(t)$ follows directly form from $\widehat{S}_{KM}(t)$:

$$\widehat{H}_{KM}(t) = -\sum_{t_{(i)} \leq t} \log\left(\frac{n_i - d_i}{n_i}\right).$$

- Problems with this estimator?

Nelson-Aalon estimator

- $\widehat{S}_{NA}(t)$ can be obtained with `coxph` of the **`survival`** package.

```
> args(coxph)
function (formula, data, weights, subset, na.action, init, control,
    ties = c("efron", "breslow", "exact"), singular.ok = TRUE,
    robust = FALSE, model = FALSE, x = FALSE, y = TRUE, tt, method = ties,
    ...)
NULL
```

- `coxph` refers to "Cox proportional hazard model" that has the form

$$h(t) = h_0(t)e^{X^\top \beta}, \tag{4}$$

where X is the covariate matrix, β is the regression coefficient, and $h_0(t)$ is called the *baseline hazard* function.

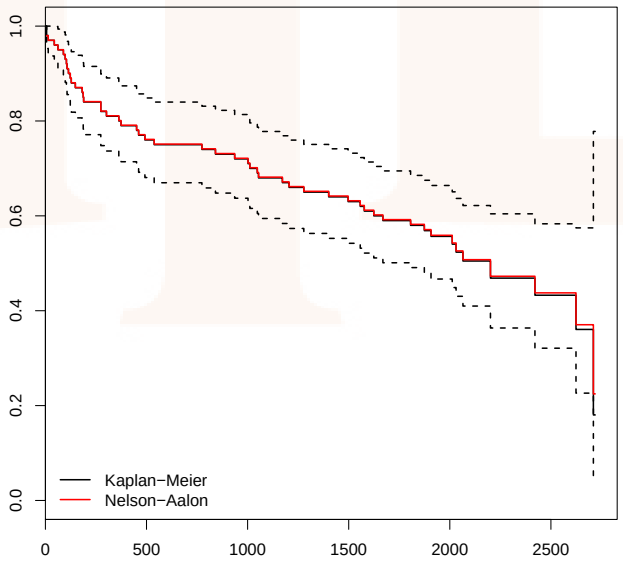
- More details will be given in Chapter 3.

Nelson-Aalon estimator

- For now, we will assume $\beta = 0$ in (4), which implies $h(t) = h_0(t)$.
- We will use $h_0(t)$ to obtain $\widehat{S}_{NA}(t)$.

```
> cox <- coxph(Surv(lenfol, fstat) ~ 1, data = whas100)
> H0 <- basehaz(cox)
> str(H0)
'data.frame': 95 obs. of  2 variables:
 $ hazard: num  0.0201 0.0303 0.0406 0.051 0.0616 ...
 $ time  : num  6 14 44 62 89 98 104 107 114 123 ...
```

```
> plot(km)
> lines(H0$time, exp(-H0$hazard), 's', col = 2)
```



Life-table estimates

- When dataset is large, the $\widehat{S}_{KM}(t)$ and $\widehat{S}_{NA}(t)$ can be obtained with intervals of time, rather than exact time points.
  - The series $\{t_{(1)}, \ldots, t_{(m)}\}$ represents intervals.
  - d_i represents the number of individual who died in $t_{(i)}$.
  - n_i represents the number of individual who are alive in $t_{(i)}$.
- Potential problem with censoring?
- Adjustments under uniform assumption (p25).
- Better to adopt methods for data with interval censoring.

Inference on $\widehat{S}_{KM}(t)$

- The 95% confidence interval (CI) does not follow the usual form of

$$\text{PE} \pm 1.96 \times \text{SE}.$$

- This is mainly because $\widehat{S}_{KM}(t)$ needs to lie between 0 and 1.
- Two common methods to obtain the 95% CI for $\widehat{S}_{KM}(t)$ are the log and log-log transformations.
- The idea is to derive the standard errors on the transformed scale first, then back-transform these back.

The Delta Method

- We need the Delta method to estimate the standard errors.
- The Delta method states that

$$\mathrm{Var}\{g(X)\} \approx \mathrm{Var}(X) \cdot \{g'(x_0)\}^2,$$

where $g'(x_0)$ is the 1st derivative of $g(\cdot)$ evaluates at constant x_0.

The Delta Method

- A special case of the Delta method is when $g(\cdot) = \log(\cdot)$.
- Setting $g(\cdot) = \log(\cdot)$, we have

$$\mathrm{Var}\{f(X)\} \approx \frac{\mathrm{Var}(X)}{x_0^2}.$$

Inference on $\widehat{S}_{KM}(t)$

- We will first look at the log transformation.
- Recall

$$\widehat{S}_{KM}(t) = \prod_{t_{(i)} \leq t} \frac{n_i - d_i}{n_i}.$$

- The variance of log-transformed $\widehat{S}_{KM}(t)$ gives

$$\text{Var}\left\{\log \widehat{S}_{KM}(t)\right\} = \text{Var}\left\{\sum_{t_{(i)} \leq t} \log\left(\frac{n_i - d_i}{n_i}\right)\right\} = \sum_{t_{(i)} \leq t} \text{Var}\left\{\log\left(\frac{n_i - d_i}{n_i}\right)\right\}.$$

- We assume independence between observations in the risk sets.
- For convenience, let's write $p_i = (n_i - d_i)/n_i$, and $\hat{p}_i$ when n_i and d_i are known.

Inference on $\widehat{S}_{KM}(t)$

- The key is to estimate $\mathrm{Var}\{\log(p_i)\}$ with the Delta method.
- For each $t_{(i)}$, n_i is fixed but d_i is random.
- $n_i - d_i$ can be assumed to follow the binomial distribution with parameters n_i and $1 - d_i/n_i$. Then

$$\mathrm{Var}(p_i) = \frac{\mathrm{Var}(n_i - d_i)}{n_i^2} = \frac{\frac{d_i}{n_i} \cdot \left(1 - \frac{d_i}{n_i}\right)}{n_i}.$$

- With the Delta method, we have

$$\mathrm{Var}\{\log(p_i)\} \approx \frac{\mathrm{Var}(p_i)}{\hat{p}_i} = \frac{d_i}{n_i \cdot (n_i - d_i)}.$$

Inference on $\widehat{S}_{KM}(t)$

- From the above result, we have

$$\text{Var}\left\{\log \widehat{S}_{KM}(t)\right\} \approx \sum_{t_{(i)} \le t} \frac{d_i}{n_i \cdot (n_i - d_i)}.$$

- By the Delta method (again),

$$\text{Var}\left\{\log \widehat{S}_{KM}(t)\right\} \approx \text{Var}\{\widehat{S}_{KM}(t)\} \cdot \frac{1}{\widehat{S}^2_{KM}(t)}.$$

- Altogether, this gives

$$\text{Var}\{\widehat{S}_{KM}(t)\} \approx \widehat{S}^2_{KM}(t) \cdot \sum_{t_{(i)} \le t} \frac{d_i}{n_i \cdot (n_i - d_i)}.$$

- This result is known as the *Greenwood's formula*, or the log transformation.
- This estimator can be obtained from a counting process approach.

Inference on $\widehat{S}_{KM}(t)$

- The Greenwood formula is the default method for `survfit`.
- With the Greenwood formula, the $100(1-\alpha)\%$ condifdence interval of $\widehat{S}_{KM}(t)$ can be obtained using the usual form of PE $\pm Z_{\alpha/2} \times$ SE.
- The bounds can still be outside of $[0, 1]$.
- An alternative approach is to consider the log-log transformation.

Inference on $\widehat{S}_{KM}(t)$

- By the Delta method, we have

$$\text{Var}\left[\log\left\{-\log \widehat{S}_{KM}(t)\right\}\right] \approx \frac{1}{\{-\log \widehat{S}_{KM}(t)\}^2} \cdot \sum_{t_{(i)} \le t} \frac{d_i}{n_i \cdot (n_i - d_i)}.$$

- This imples that the $100(1-\alpha)\%$ condifdence interval can be constructed by inversing

$$\log\{-\log \widehat{S}_{KM}(t)\} \pm Z_{\alpha/2} \times \text{SE}\left[\log\{-\log \widehat{S}_{KM}(t)\}\right]$$

- Since $-\log$ of a survival function gives the cumulative hazard function, e.g., $-\log S(t) = H(t)$, the log-log approach called the "log hazard" approach.

Inference on $\widehat{S}_{KM}(t)$

- Types of CI can be specified with `conf.type` in `survfit`.

```
> ?survfit.coxph
```

- Some options are available for `conf.type` depending on $g(\cdot)$ used in the Delta method.

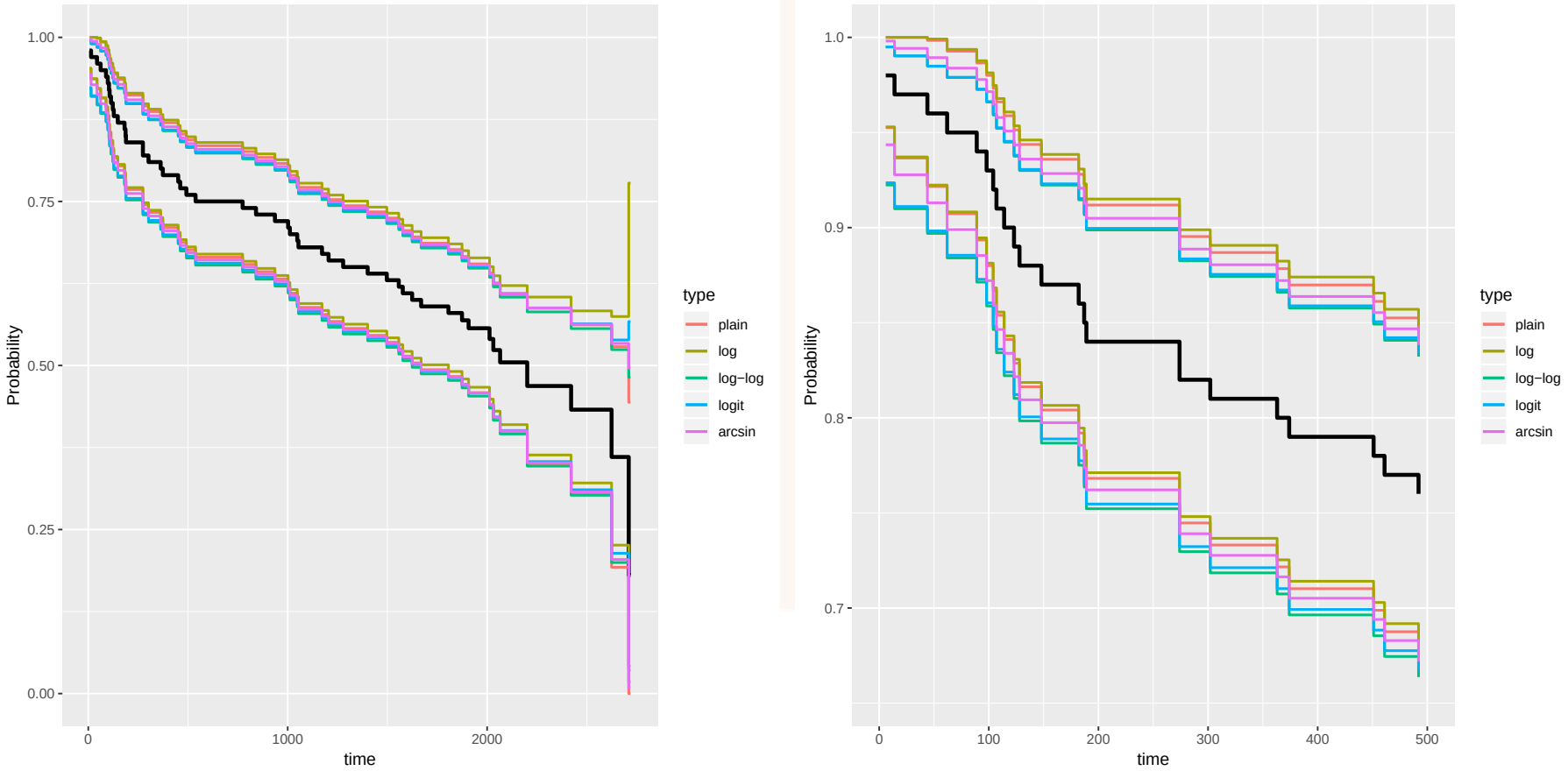
$$\begin{aligned}
\texttt{plain} \quad & g(x) = x \\
\texttt{log} \quad & g(x) = \log(x) \\
\texttt{log-log} \quad & g(x) = \log\{-\log(x)\} \\
\texttt{logit} \quad & g(x) = \log\left(\frac{x}{1-x}\right) \\
\texttt{arcsin} \quad & g(x) = \arcsin\sqrt{(x)}
\end{aligned}$$

- In addition, Peto et al. (1977) proposed to estimate $\text{Var}\{\widehat{S}_{KM}(t)\}$ from

$$\text{Var}\{\widehat{S}_{KM}(t)\} = \frac{\widehat{S}_{KM}(t) \cdot (1 - \widehat{S}_{KM}(t))}{n_i}$$

Inference on $\widehat{S}_{KM}(t)$

- The following depict $\widehat{S}_{KM}(t)$ with the five `conf.type`'s for `whas100`.
- The CI's are quite close to each other.



*Inference on the median and percentiles

- Given a $\widehat{S}(t)$ ($\widehat{S}_{KM}(t)$ or $\widehat{S}_{NA}(t)$), the estimate of the pth percentile is

$$\hat{t}_p = \min\{t : \hat{S}(t) \leq (p/100)\}.$$

- The Delta method can be used again to obtain $\mathrm{Var}(\hat{t}_p)$.
- Setting $g(\cdot) = S(\cdot)$, we have the relationship

$$\mathrm{Var}\{\widehat{S}(\hat{t}_p)\} \approx \mathrm{Var}(\hat{t}_p) \cdot \{f(\hat{t}_p)\}^2,$$

  where $f(t) = \mathrm{d}\widehat{S}(t)/\mathrm{d}t$.
- The only unknown in the above equation is $f(t)$, which can be approximated by linear interpolation:

$$\hat{f}(\hat{t}_p) \approx \frac{\widehat{S}(\hat{u}_p) - \widehat{S}(\hat{l}_p)}{\hat{l}_p - \hat{u}_p},$$

  where $\hat{u}_p < \hat{t}_p < \hat{l}_p$, $\hat{u}_p = \max\{t : \widehat{S}(t) \geq p/100 + \epsilon\}$ and $\hat{l}_p = \min\{t : \widehat{S}(t) \leq p/100 - \epsilon\}$, for some small constant ϵ.

*Inference on the median and percentiles

- Replacing the unknown quantities with their empirical estimates, the $100(1-\alpha)\%$ CI can be obtained through $\hat{t}_p \pm Z_{\alpha/2} \times \mathrm{SE}(\hat{t}_p)$.
- Clinicians are specifically interested in median survival (follow-up) time, because survival time data often tend to skewed to the right.
- Other quantity of interest is the semi-interquartiles range (SIQR):

$$\mathrm{SIQR} = \frac{t_{75} - t_{25}}{2}.$$

- Like the variance, the larger the SIQR, the more dispersed is the survival time distribution.

*Inference on the median and percentiles

- Median survival time is printed by `survfit`.

```
> survfit(Surv(lenfol, fstat) ~ 1, data = whas100)
Call: survfit(formula = Surv(lenfol, fstat) ~ 1, data = whas100)

      n  events  median 0.95LCL 0.95UCL
    100      51    2201    1806      NA
```

- Median follow-up time does not always exists.

```
> survfit(Surv(lenfol, fstat) ~ 1, data = whas100[81:100,])
Call: survfit(formula = Surv(lenfol, fstat) ~ 1, data = whas100[81:100,
    ])

      n  events  median 0.95LCL 0.95UCL
     20       9      NA    1577      NA
```

- A more practical approach?

Counting processes

- As is seen from before, the focus in survival analysis is on observing the occurrence of events over time.
- Such occurrences constitute point (counting) process; counting number of events as they come along.
- There is a very neat collection of theories for counting processes.
- More in-depth details can be found in Fleming and Harrington (2011); Kalbfleisch and Prentice (2011).

Counting processes

- Appendix 2 gives a short introduction of counting processes, in the case of right censoring.
- We start by focusing on a *single type* of event without censoring.
- For a given time t, let $N(t)$ be the number of events over the time period $(0, t]$, then $N(t)$ is a counting process.
- The counting process $N(t)$ is *continuous from the right*, with jump size 1.

Poisson process

- A well-known example of a counting process is the homogeneous Poisson process.
- Jumps occur randomly and independently of each other (independent increment property).
- A homogeneous Poisson process is described by its *intensity* λ.
- The λ is the probability of occurrence of an event in a small interval divided by the length of the interval.
- We will apply this idea to modeling counting process.

Counting processes

- Suppose the intensity function that describes $N(t)$ is $\lambda(t)$.
- Under our assumption that a subject can experience at most one event, consider a small time interval $[t, t + \mathrm{d}t)$, $\lambda(t)$ is

$$\lambda(t)\mathrm{d}t = \mathrm{P}(\mathrm{d}N(t) = 1|\text{past}),$$

  where $\mathrm{d}N(t)$ denotes the # of events in $[t, t + dt)$, or $N(t + \mathrm{d}t) - N(t)$.
- Formally speaking, the "past" represents the *filtration* of the process up to but not including time t.

Counting processes

- Under our assumption, $\mathrm{d}N(t)$ is binary, and

$$\lambda(t)\mathrm{d}t = \mathrm{E}\{\mathrm{I}(\mathrm{d}N(t) = 1)|\text{past}\} = \mathrm{E}\{\mathrm{d}N(t)|\text{past}\}.$$

- Then it follows

$$\mathrm{E}(\mathrm{d}N(t) - \lambda(t)\mathrm{d}t|past) = 0. \tag{5}$$

- If we define a new process

$$M(t) = N(t) - \int_0^t \lambda(s)\mathrm{d}s, \tag{6}$$

  then we have $\mathrm{E}(\mathrm{d}M(t)|past) = 0$.
- It turns out $M(t)$ is a zero-mean martingale.

Counting processes

- Definition (6) can be written as

$$\mathrm{d}N(t) = \lambda(t)\mathrm{d}t + \mathrm{d}M(t), \tag{7}$$

  reflecting the relationship *observation = signal + noise*.
- Think of $M(t)$ as the sum of random errors.
- Let

$$\Lambda(t) = \int_0^t \lambda(s)\mathrm{d}s,$$

  (5) and (6) implies $\Lambda(t)$ is the cumulative expected # of events in $(0, t]$, or $\Lambda(t) = \mathrm{E}\{N(t)\}$.
- $\Lambda(t)$ versus $H(t)$?

Counting processes

- Now we will look at the scenario when there is only *one event type* and a subject can experience *at most one event* (no ties in event times).
- In this case, the counting process $N(t) = \mathrm{I}(T \leq t)$, where T is the survival time with hazard $h(t)$.
- The $N(t)$ defined above has a jump size 1 at T.
- We then have

$$\mathrm{P}(\mathrm{d}N(t) = 1|\text{past}) = \begin{cases} h(t)\mathrm{d}t & \text{if } T \geq t \\ 0 & \text{if } T < t \end{cases} = h(t)\mathrm{I}(T \geq t)\mathrm{d}t.$$

- The relationship above implies the intensity process $\lambda(t) = h(t) \cdot \mathrm{I}(T \geq t)$.

Counting processes

- Building onto our assumption, now assume we have *n independent subjects*, each with T_i, $i = 1, \ldots, n$, and hazard $h_i(t)$.
- Suppose $h_i(t) = h(t)$ for all i.
- From the last example, we have

$$N_i(t) = \mathrm{I}(T_i \leq t) \text{ and } \lambda_i(t) = h_i(t)\mathrm{I}(T_i \geq t).$$

- Define the *aggregated* process by adding together the individual processes:

$$N(t) = \sum_{i=1}^{n} N_i(t).$$

- This process counts the # of individuals who experienced the event by t.
- Is $N(t)$ here a proper counting process?

Counting processes

- Assuming continuous survival times, and the aggregated processs jumps one unit at a time,

$$\mathrm{E}(\mathrm{d}N(t)|\text{past}) = \sum_{i=1}^{n} \mathrm{E}(\mathrm{d}N_i(t)|\text{past})$$

  implies the aggregated intensity satisfies $\lambda(t)\mathrm{d}t = \sum_{i=1}^{n} \lambda_i(t)\mathrm{d}t$ and

$$\lambda(t) = h(t)\,Y(t),$$

  where $Y(t) = \sum_{i=1}^{n} \mathrm{I}(T_i \geq t)$ is the number of individuals at risk right before t, e.g., $Y(t) = n - N(t^-)$.
- Plug $\lambda(t)$ into Equation (7) gives the Nelson-Aalen estimator for $H(t)$.

Derivation of $\widehat{H}_{NA}(t)$

- Plug $\lambda(t)$ into Equation (7), we have

$$\mathrm{d}N(t) = h(t)Y(t)\mathrm{d}t + \mathrm{d}M(t)$$

- Intergrating both side after diving by $Y(t)$ gives

$$\int_0^t \frac{1}{Y(t)}\mathrm{d}N(t) - \int_0^t h(t)\mathrm{d}t = \int_0^t \frac{1}{Y(t)}\mathrm{d}M(t)$$

- The right-hand side is a stochastic integral with respect to a zero-mean martingale.
- The first term in the left-hand side gives $\widehat{H}_{NA}(t) = \sum_{t_{(i)} \le t} \frac{1}{n_i}$.
- Then $\mathrm{E}\left\{\widehat{H}_{NA}(t) - \widehat{H}(t)\right\} = 0$ and $\widehat{H}_{NA}(t)$ is an unbiased estimator of $\widehat{H}(t)$.
- The variance estimator can be derived using the *variation processes* or with transformation through the Delta methods.

Counting processes

- Consider the same assumptions but allowing ties in event times.
- Two common approaches to deal with tied event times depend on how tied event times arise.
  1. Two event times coincide due to rounding.

$$\widehat{H}_{NA}(t) = \sum_{t_{(i)} \le t} \sum_{k=1}^{d_i} \frac{1}{n_i - k}.$$

  2. Event times are genuinely discrete, so that tied event times are real and not due to rounding.

$$\widehat{H}_{NA}(t) = \sum_{t_{(i)} \le t} \frac{d_i}{n_i}.$$

- More discussion on large number properties with tied event times can be found in Anderson et al. (1993).

Counting processes

- For nonparametric or semi-parametric methods, we do not need to have a distributional assumption on the censoring time, C.
- Rather, we will assume independent censoring:

$$\mathrm{P}(t \leq \tilde{T}_i < t + \mathrm{d}t, \Delta_i = 1 | \tilde{T}_i \geq t, \text{past}) = \mathrm{P}(t \leq T_i < t + \mathrm{d}t | T_i \geq t),$$

  where $\tilde{T}_i = \min(T_i, C_i)$ and $\Delta_i = \mathrm{I}(T_i < C_i)$, for $i = 1, \ldots, n$.
- In the presense of right censoring, the counting process is specified as

$$N_i(t) = \mathrm{I}\{\tilde{T}_i \leq t, \Delta_i = 1\}, i = 1, \ldots, n,$$

  and $\lambda_i(t)\mathrm{d}t = \mathrm{P}(\mathrm{d}N_i(t) = 1 | \text{past})$.
- Applying the independent censoring assumption, the intensity process for $N_i(t)$ takes the form $\lambda_i(t) = h_i(t)Y_i(t)$, where $Y_i(t) = \mathrm{I}(\tilde{T}_i \geq t)$ is the at risk indicator for individual i.

Counting processes

- As in the uncensored example, the *aggregated* process is

$$N(t) = \sum_{i=1}^{n} N_i(t) = \sum_{i=1}^{n} \mathrm{I}(\tilde{T}_i \leq t, \Delta_i = 1),$$

  and the *aggregated* intensity process is

$$\lambda(t) = \sum_{i=1}^{n} \lambda_i(t) = \sum_{i=1}^{n} h_i(t) Y_i(t).$$

- In the case where $h_i(t) = h(t)$ for all i, the intensity process takes the form $\lambda(t) = h(t)Y(t)$, where $Y(t) = \sum_{i=1}^{n} Y_i(t)$.
- The Nelson-Aalen estimator can be derived similarly.

Counting processes

- Counting processes are non-decreasing.
- Martingales associated with $M(t)$ are sub-martingales.
- Doob-Meyer decomposition guarantees the relationship

$$N(t) = h(t)Y(t) + M(t).$$

- Martingale central limit theorem.

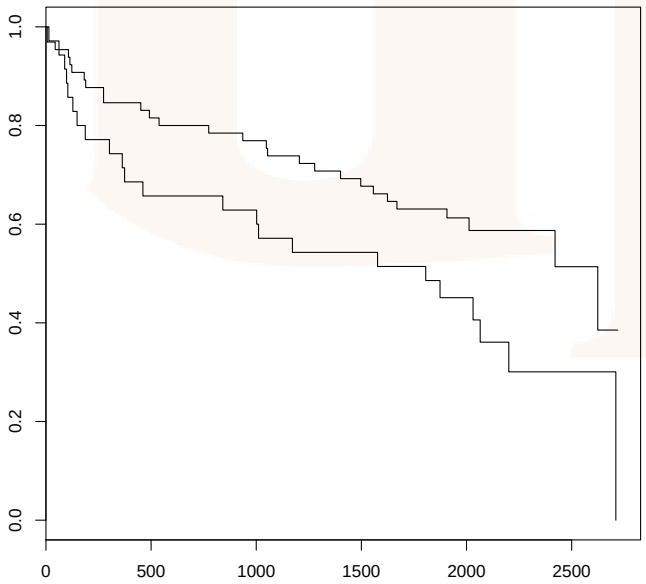
Comparison of survival functions

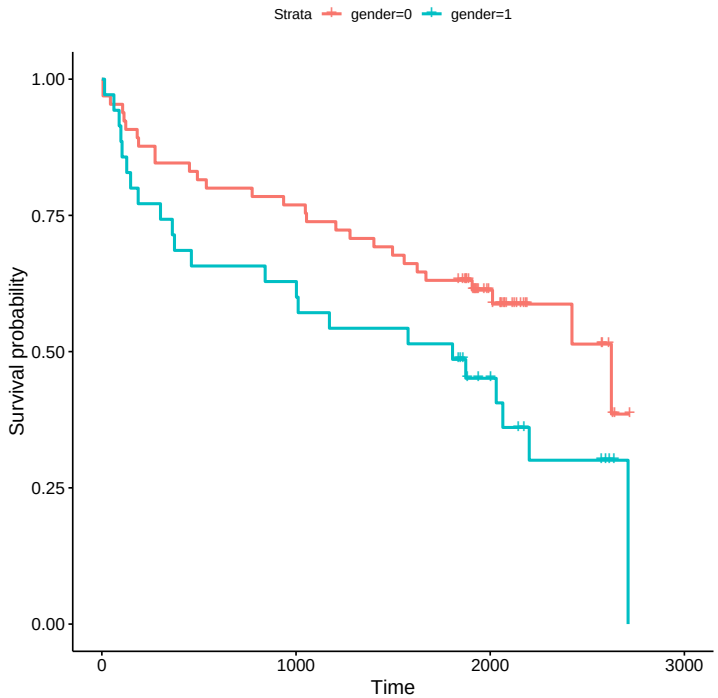
- The simplest way of comparing the survival functions is to plot them on the same axe.

```
> km <- survfit(Surv(lenfol, fstat) ~ gender, data = whas100)
> km
Call: survfit(formula = Surv(lenfol, fstat) ~ gender, data = whas100)

           n events median 0.95LCL 0.95UCL
gender=0 65     28   2624    2012      NA
gender=1 35     23   1806     841      NA
```

- `ggsurvplot` gives more informative output.





Comparison of survival functions

- In the `whas100` study, the survival function for female patients (`gender = 0`) is always greater than that for male patients.
- Two explanations for the observed difference:
  - A real difference between the survival times of the two groups.
  - The difference has been observed is the result of chance variation.
- Procedures such as the *hypothesis test* is needed to distinguish the two possible explanations.

Hypothesis testing

- As the hypothesis tests commonly encountered, the testing procedure here consists of the following major steps:
  1. State the *null hypothesis* and the *alternative hypothesis*.
  2. Formulate a *test statistic* that measures the extent to which the observed data depart from the null hypothesis.
  3. Calculate the *p*-value; the probability of obtaining a value as extreme or more extreme than the observed value, when the null hypothesis is true.

Hypothesis testing

- p-value can be interpreted as a measure of the strength of evidence against the null hypothesis.
- A p-value of 0.000 should be interpreted as $p < 0.001$.
- A one-sided hypothesis test is only appropriate when there is no interest in departures from the null hypothesis in the opposite direction.
- We will look at non-parametric procedures including the log-rank test and the Wilcoxon test.

The log-rank test

- If we are willing to assume survival data follow a particular parametric distribution, we can construct a test based on likelihood theory.
- We will derive a nonparametric test using a rank-based procedure.
- Suppose the population survival curves are $S_1(t)$ and $S_0(t)$.
- Ideally, we would like to test $H_o : S_1(t) = S_0(t)$ versus $H_a : S_1(t) > S_0(t)$, $S_1(t) < S_0(t)$, or $S_1(t) \neq S_0(t)$.
- Unfortunately, this is difficult because H_a can take a wide range of forms.
- Instead, it is more feasible to consider the *Lehman alternative*:

$$H_a : S_1(t) = [S_0(t)]^{\theta}, \text{ for } \theta > 0. \tag{8}$$

The log-rank test

- The hypothesis in (8) can be view in terms of the hazard functions:

$$H_o : \lambda_1(t) = \lambda_0(t) \text{ versus } H_a : \lambda_1(t) = \theta\lambda_0(t).$$

- Either way, we could rewrite the hypothesis test as

$$H_o : \theta = 1 \text{ versus } H_a : \theta > 1, \text{ or } \theta < 1, \text{ or } \theta \neq 1.$$

- One can interpret the results solely based on θ too.
- For example, under $H_a : \theta > 1$, then
  - $S_1(t)$ will be uniformly lower than $S_0(t)$.
  - $h_1(t)$ will be uniformly higher than $h_0(t)$.

The log-rank test

- Following the notations defined previously, we assume
  - the two independent random samples are of size N_0 and N_1.
  - D is the total number of events in the combined sample (size $N_0 + N_1$).
  - $\{t_{(1)}, \ldots, t_{(D)}\}$ is the ordered event times.
  - Let d_{0i} and d_{1i} are the number of events in group 0 and 1, respectively.
  - Let n_{0i} and n_{1i} are the number of at risk in group 0 and 1, respectively.

The log-rank test

- For the ith event time, we construct the following two-by-two table:

	Group 1	Group 0	Total
Failure	d_{1i}	d_{0i}	d_i
Non-failure	$n_{1i} - d_{1i}$	$n_{0i} - d_{0i}$	$n_i - d_i$
At risk	n_{1i}	n_{0i}	n_i

- Suppose the numbers of failures in two groups are independent, holding the margins fixed, then the distribution of d_{1i} (or d_{0i}) follows a *hypergeometric distribution*.
- This gives

$$\mathrm{E}(d_{1i}) = \frac{n_{1i} \cdot d_i}{n_i}, \text{ and } \mathrm{Var}(d_{1i}) = \frac{n_{1i} \cdot n_{0i} \cdot d_i \cdot (n_i - d_i)}{n_i^2 \cdot (n_i - 1)}.$$

The log-rank test

- Using the idea from the χ^2 tests, the test statistic has the form

$$Q = \frac{\left[\sum_{i=1}^{D} \omega_i \{d_{1i} - \mathrm{E}(d_{1i})\}\right]^2}{\sum_{i=1}^{D} \omega_i^2 \mathrm{Var}(d_{1i})}, \tag{9}$$

  where ω_i is a possibly data-dependent weight.
- When there is no tied failure times, $\mathrm{Var}(d_{1i}) = \frac{n_{1i} \cdot n_{0i}}{n_i^2}$.
- Under the null, Q follows the χ^2 distribution with one degree of freedom.
- The log-rank test sets $\omega_i = 1$ (Peto and Peto, 1972).

The log-rank test

- Different selections of ω_i were studied.
- Most common expression has the form of

$$\omega_i = \left\{ \hat{S}(t_{(i)}) \right\}^{\rho}, \text{ for } \rho \in [0, 1],$$

  where $\hat{S}(t)$ is the survival estimator from the combined sample, ignoring group.
- This is called the Fleming-Harrington $G(\rho)$ test (e.g. Cox and Oakes, 1984; Harrington and Fleming, 1982).
  - $\rho = 0$ gives the log-rank test
  - $\rho = 1$ gives the Wilcoxon test.
  - $\rho = 0.5$ gives the Tarone and Ware (1977) test.

The log-rank test

- The $G(\rho)$ test is implemented in `survdiff` of the **`survival`** package

```
> args(survdiff)
function (formula, data, subset, na.action, rho = 0)
NULL
> survdiff(Surv(lenfol, fstat) ~ gender, data = whas100)
Call:
survdiff(formula = Surv(lenfol, fstat) ~ gender, data = whas100)

          N Observed Expected (O-E)^2/E (O-E)^2/V
gender=0 65       28     34.6      1.27      3.97
gender=1 35       23     16.4      2.68      3.97

 Chisq= 4  on 1 degrees of freedom, p= 0.05
```

- The log-rank test shows `gender` is marginally significant at $\alpha = 0.05$.

The log-rank test

- Varying ρ shows similar results here.
- In general, when the tests give different results, then more than one result should be reported.
- It is important to also consult the plot to ascertain the directional effect of stratification or treatment.

The log-rank test

- As in the Pearson's χ^2 test, a continuity correction could be considered when sample sizes are too small:

$$Q^* = \frac{\left[\sum_{i=1}^{D} \omega_i \{|d_{1i} - \mathrm{E}(d_{1i})| - 0.5\}\right]^2}{\sum_{i=1}^{D} \omega_i^2 \mathrm{Var}(d_{1i})}.$$

The log-rank test

- A problem can occur if the estimated survival (hazard) functions cross one another.
- This is similar to the proportional hazard assumption in the Cox models.
- In `whas100` data, the two survival curves (by gener) crossed one another at early t, despite being so different in large t.
- Fleming et al. (1987) proposed supremum versions of the log-rank tests, but have not been implemented in any software packages.

The log-rank test

- The tests discussed here can be extended to comparison more than two survival functions simultaneously.
- K-by-K tables instead of two-by-two tables at each event time.
- When there are many groups to compare, it might be more convenient to consider regression models.

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