

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 $F(t) = P(T \leq t)$.
- The survival function of T is then defined as

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

- 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

$$h(t) = \lim_{dt \rightarrow 0} \frac{P(t \leq T < t + dt | T \geq t)}{dt}. \quad (1)$$

- $P(t \leq T < t + dt | T \geq t)$ is a conditional probability.
- The conditional probability is then expressed as a probability per unit time by dividing by the time interval, dt , 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 $dt = 1$.
 - $\lim_{dt \rightarrow 0}$ 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 $E\{I(\cdot)\} = P(\cdot)$.
 - 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:

$$(1) = \lim_{dt \rightarrow 0} \frac{P(t \leq T < t + dt)}{dt \cdot P(T \geq t)} = \lim_{dt \rightarrow 0} \frac{F(t + dt) - F(t)}{dt} \cdot \frac{1}{P(T \geq t)} = \frac{dF(t)}{dt} \cdot \frac{1}{S(t)}.$$

- $h(t)$ 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

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

- 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

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

where $H(t) = \int_0^t h(u) du$ 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

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

- 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
```

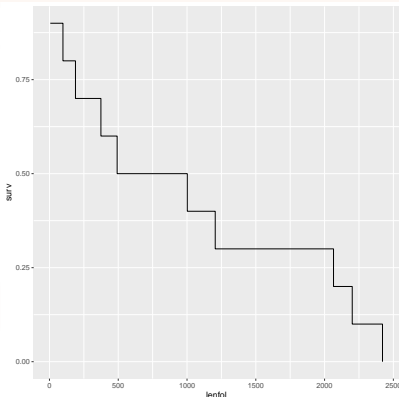
A tibble: 10 x 10

	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)
```

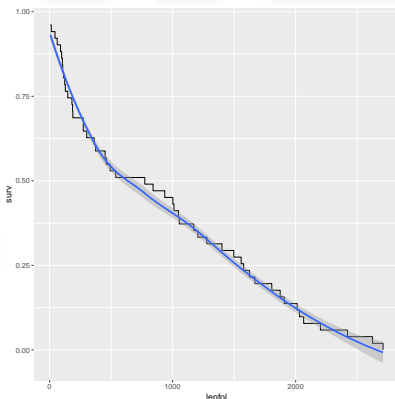


- The $\hat{S}_e(t)$ is 1 at $t = 0$ and 0 at the final death time.
- The $\hat{S}_e(t)$ is assumed to be constant between adjacent death times.

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 estimator

- 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 $P(T > t)$ by conditioning on prior times.
- Suppose a sample size of n , $P(T > t)$ can be decomposed as

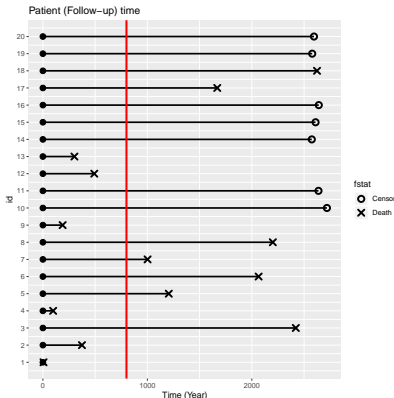
$$\hat{S}_{KM}(t) \doteq P(T > t) = P(T > t_{(0)}) \cdot P(T > t_{(1)} | T > t_{(0)}) \cdot P(T > t_{(2)} | T > t_{(1)}) \cdot \dots \cdot P(T > t | T > t_{(i)}),$$

for a series of time intervals $0 \doteq t_{(0)} < t_{(1)} < \dots < t_{(i)} < t$ for some $i \leq n$.

- In general, the series $\{t_{(1)}, \dots, t_{(m)}\}$ denotes the m ordered death times.

Kaplan-Meier estimator

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



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

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

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

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

Kaplan-Meier estimator

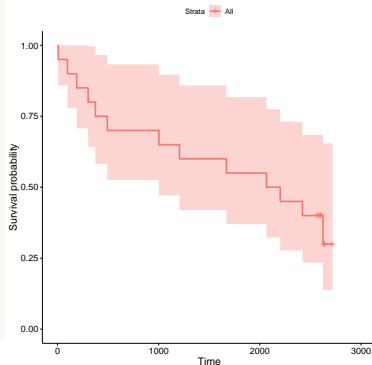
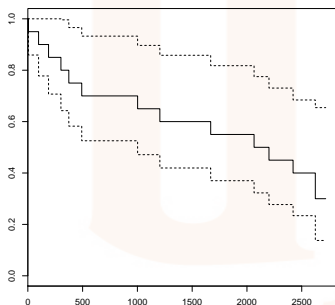
- The Kaplan-Meier estimator can be obtained with the `survfit` function.

```
> 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

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

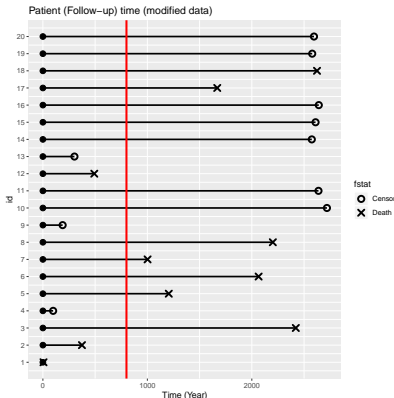
```
> library(survminer)
> plot(km)
> ggsurvplot(km)
```



- 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 $P(T > 800)$ based on the following modified data:



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

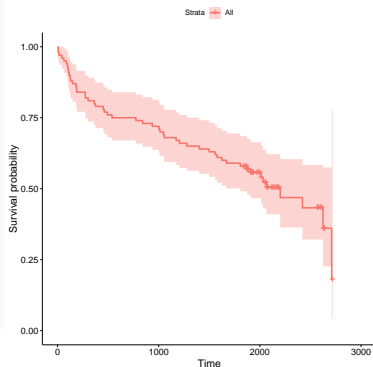
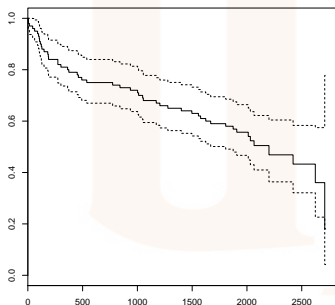
$t_{(0)}$	$t_{(1)}$	$t_{(2)}$	$t_{(3)}$
0	6	374	492
- In this modified data, $t = 98, 189, 302$ are considered as censored.

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

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 $(t_i, c_i), i = 1, 2, \dots, n$.
- Suppose there are m deaths and $m \leq n$.
- The series $\{t_{(1)}, \dots, t_{(m)}\}$ are the m ordered death times.
- The Kaplan-Meier estimator has the form

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

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-Aalen estimator

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

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

- 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

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

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

Nelson-Aalen estimator

- $\hat{S}_{NA}(t)$ 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 $\hat{H}_{NA}(t)$, or $\hat{H}_{KM}(t) = -\log \hat{S}_{KM}(t)$.
- The $\hat{H}_{KM}(t)$ follows directly from $\hat{S}_{KM}(t)$:

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

- Problems with this estimator?

Nelson-Aalen estimator

- $\hat{S}_{NA}(t)$ 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

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

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

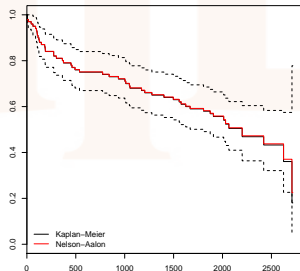
- More details will be given in Chapter 3.

Nelson-Aalen 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 $\hat{S}_{NA}(t)$.

```
> 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 $\hat{S}_{KM}(t)$ and $\hat{S}_{NA}(t)$ can be obtained with intervals of time, rather than exact time points.
 - The series $\{t_{(1)}, \dots, t_{(m)}\}$ 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 $\hat{S}_{KM}(t)$

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

$$PE \pm 1.96 \times SE.$$

- This is mainly because $\hat{S}_{KM}(t)$ needs to lie between 0 and 1.
- Two common methods to obtain the 95% CI for $\hat{S}_{KM}(t)$ 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

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

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

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

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

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

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

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

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

- 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 $\hat{S}_{KM}(t)$

- The key is to estimate $\text{Var}\{\log(p_i)\}$ 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

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

- With the Delta method, we have

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

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

- From the above result, we have

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

- By the Delta method (again),

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

- Altogether, this gives

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

- 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 $\hat{S}_{KM}(t)$

- The Greenwood formula is the default method for `survfit`.
- With the Greenwood formula, the $100(1 - \alpha)\%$ confidence interval of $\hat{S}_{KM}(t)$ 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 $\hat{S}_{KM}(t)$

- By the Delta method, we have

$$\text{Var} \left[\log \left\{ -\log \hat{S}_{KM}(t) \right\} \right] \approx \frac{1}{\{-\log \hat{S}_{KM}(t)\}^2} \cdot \sum_{t_{(j)} \leq t} \frac{d_j}{n_j \cdot (n_j - d_j)}.$$

- This implies that the $100(1 - \alpha)\%$ confidence interval can be constructed by inverting

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

- 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 $\hat{S}_{KM}(t)$

- 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.

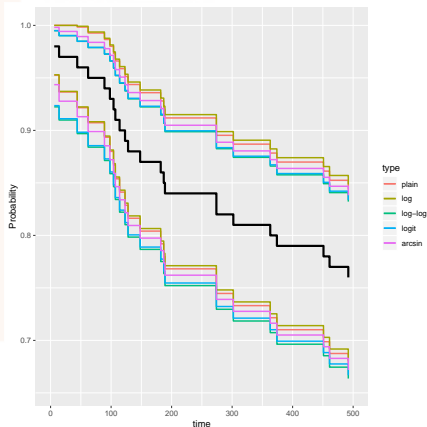
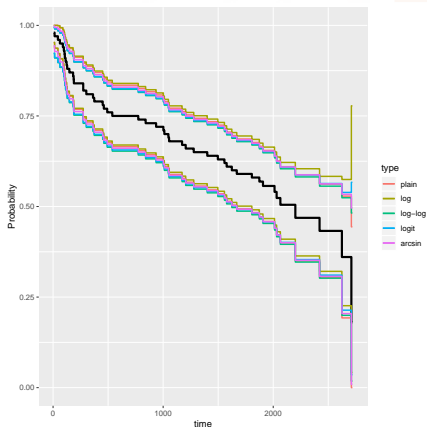
```
plain   $g(x) = x$ 
log      $g(x) = \log(x)$ 
log-log  $g(x) = \log\{-\log(x)\}$ 
logit    $g(x) = \log\left(\frac{x}{1-x}\right)$ 
arcsin   $g(x) = \arcsin \sqrt{x}$ 
```

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

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

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

- The following depict $\hat{S}_{KM}(t)$ 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 $\hat{S}(t)$ ($\hat{S}_{KM}(t)$ or $\hat{S}_{NA}(t)$), the estimate of the p th percentile is

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

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

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

where $f(t) = d\hat{S}(t)/dt$.

- The only unknown in the above equation is $f(t)$, which can be approximated by linear interpolation:

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

where $\hat{u}_p < \hat{t}_p < \hat{l}_p$, $\hat{u}_p = \max\{t : \hat{S}(t) \geq p/100 + \epsilon\}$ and $\hat{l}_p = \min\{t : \hat{S}(t) \leq p/100 - \epsilon\}$, 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 $\hat{t}_p \pm Z_{\alpha/2} \times \text{SE}(\hat{t}_p)$.
- Clinicians are specifically interested in median survival (follow-up) time, because survival time data often tend to be skewed to the right.
- Other quantity of interest is the semi-interquartiles range (SIQR):

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

- 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 $[t, t + dt)$, $\lambda(t)$ is

$$\lambda(t)dt = P(dN(t) = 1 | \text{past}),$$

where $dN(t)$ denotes the # of events in $[t, t + dt)$, or $N(t + dt) - N(t)$.

- Formally speaking, the “past” represents the *filtration* of the process up to but not including time t .

Counting processes

- Under our assumption, $dN(t)$ is binary, and

$$\lambda(t)dt = E\{I(dN(t) = 1)|past\} = E\{dN(t)|past\}.$$

- Then it follows

$$E(dN(t) - \lambda(t)dt|past) = 0. \quad (5)$$

- If we define a new process

$$M(t) = N(t) - \int_0^t \lambda(s)ds, \quad (6)$$

then we have $E(dM(t)|past) = 0$.

- It turns out $M(t)$ is a zero-mean martingale.

Counting processes

- Definition (6) can be written as

$$dN(t) = \lambda(t)dt + dM(t), \quad (7)$$

reflecting the relationship *observation = signal + noise*.

- Think of $M(t)$ as the sum of random errors.
- Let

$$\Lambda(t) = \int_0^t \lambda(s)ds,$$

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

- $\Lambda(t)$ 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 $N(t) = I(T \leq t)$, 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

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

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

Counting processes

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

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

- 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 process jumps one unit at a time,

$$E(dN(t)|\text{past}) = \sum_{i=1}^n E(dN_i(t)|\text{past})$$

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

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

where $Y(t) = \sum_{i=1}^n I(T_i \geq t)$ 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 $\hat{H}_{NA}(t)$

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

$$dN(t) = h(t)Y(t)dt + dM(t)$$

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

$$\int_0^t \frac{1}{Y(s)} dN(s) - \int_0^t h(s) ds = \int_0^t \frac{1}{Y(s)} dM(s)$$

- The right-hand side is a stochastic integral with respect to a zero-mean martingale.
- The first term in the left-hand side gives $\hat{H}_{NA}(t) = \sum_{t_{(i)} \leq t} \frac{1}{n_i}$.
- Then $E \left\{ \hat{H}_{NA}(t) - H(t) \right\} = 0$ and $\hat{H}_{NA}(t)$ is an unbiased estimator of $H(t)$.
- 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.
 - Two event times coincide due to rounding.

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

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

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

- 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:

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

where $\tilde{T}_i = \min(T_i, C_i)$ and $\Delta_i = I(T_i < C_i)$, for $i = 1, \dots, n$.

- In the presense of right censoring, the counting process is specified as

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

and $\lambda_i(t)dt = P(dN_i(t) = 1 | \text{past})$.

- 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 $Y_i(t) = I(\tilde{T}_i \geq t)$ is the at risk indicator for individual i .

Counting processes

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

$$N(t) = \sum_{i=1}^n N_i(t) = \sum_{i=1}^n \mathbf{I}(T_i \leq t, \Delta_i = 1),$$

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

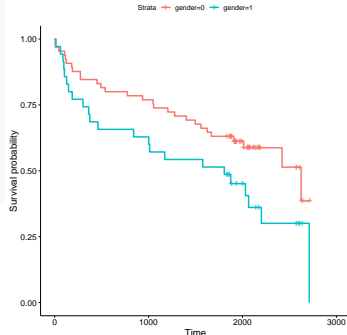
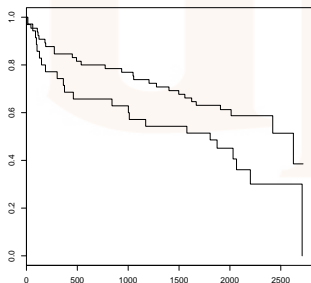
- The simplest way of comparing the survival functions is to plot them on the same axe.

```
> 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*:

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

The log-rank test

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

$$H_o : h_1(t) = h_0(t) \text{ versus } H_a : h_1(t) = \theta h_0(t).$$

- 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 $N_0 + N_1$).
 - $\{t_{(1)}, \dots, t_{(D)}\}$ 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 i th 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

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

The log-rank test

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

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

where ω_i is a possibly data-dependent weight.

- When there is no tied failure times, $\text{Var}(d_{1i}) = \frac{n_{1i} \cdot n_{0i}}{n_i^2}$.
- 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 `survdif` of the **survival** package

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

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

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 gender) 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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