# Survival Analysis: Weeks 2-3

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# Kaplan-Meier(KM) Estimator

- Nonparametric estimation of the survival function $S(t) = \mathrm{pr}(T > t)$
- The nonparametric estimation is more robust and does not depend on any parametric assumption.

# If there is no censoring

- $S(t)$ can be consistently estimated by

$$\hat{S}(t) = n^{-1} \sum_{i=1}^{n} I(T_i > t).$$

- $\hat{S}$ is a discrete distribution with mass probability of $n^{-1}$ at observed times $T_1, \cdots, T_n$

- $\hat{S}(t)$ is the nonparametric maximum likelihood estimator (NPMLE) for $S(t)$.

# CDF as NPMLE

- Assuming that $F(\cdot)$ is discrete with mass probability at $T_1 < T_2 < \cdots < T_n$, where $\{T_1, T_2, \cdots\}$ are observed times.
- Let $f_1 = \mathrm{pr}(T = T_1), f_2 = \mathrm{pr}(T = T_2), \cdots$ .
- Objective: estimate $f_1, f_2, \cdots$ .
- Method: maximize $\prod_{i=1}^{n} f_i$ subject to $\sum_{i=1}^{n} f_i = 1$.
- Solution: $\hat{f}_1 = \hat{f}_2 = \cdots = \hat{f}_n = n^{-1}$.

# Data and Assumptions

- Data: $\{(U_i, \delta_i), i = 1, \cdots, n\}$ where $U_i = \min(T_i, C_i)$ and $\delta_i = I(T_i \leq C_i)$.
- Assumptions:
  1. $T_1, \cdots, T_n$ i.i.d. $\sim F(\cdot) = 1 - S(\cdot)$
  2. $C_1, \cdots, C_n$ i.i.d. $\sim G(\cdot)$
  3. $T_i \perp C_i, i = 1, \cdots, n$. Noninformative censoring!

## If there is censoring

- Assuming that $F(\cdot)$ is discrete with mass probability at $v_1 < v_2 < \cdots$ , where $\{v_1, v_2, \cdots\}$ are observed times.
- Let $f_1 = \mathrm{pr}(T = v_1), f_2 = \mathrm{pr}(T = v_2), \cdots$ .
- Objective: estimate $f_1, f_2, \cdots$ .

# Example

- Obs: $2, 2, 3^+, 5, 5^+, 7, 9, 16, 16, 18^+$, where $^+$ means censored
- $v_1 = 2; v_2 = 3, v_3 = 5, v_4 = 7, v_5 = 9, v_6 = 16, v_7 = 18, v_8 = 18^+$
- The likelihood function in terms of $(f_1, f_2, \cdots)$ :

  $$L(F) = f_1^2(f_3+f_4+f_5+f_6+f_7+f_8)f_3(f_4+f_5+f_6+f_7+f_8)f_4 f_5 f_6^2 f_8,$$

  where $f_1 + f_2 + f_3 + f_4 + f_5 + f_6 + f_7 + f_8 = 1$

# Reparametrization tricks

- The discrete hazard function: $h_1 = \mathrm{pr}(T = v_1)$ and $h_j = \mathrm{pr}(T = v_j | T > v_{j-1}), j > 2$
- For $t \in [v_j, v_{j+1})$

$$S(t) = \mathrm{pr}(T > t) = \mathrm{pr}(T > v_j) = \prod_{i=1}^{j} (1 - h_i).$$

- For $t = v_j$

$$f_j = f(t) = \mathrm{pr}(T = t) = h_j \prod_{i=1}^{j-1} (1 - h_i).$$

# Reparametrization tricks

- The likelihood function in terms of $(h_1, h_2, \cdots)$ :

$$
\begin{aligned}
L(F) =& h_1^2 \times \{(1-h_1)(1-h_2)\} \times \{(1-h_1)(1-h_2)h_3\} \\
& \times \{(1-h_1)(1-h_2)(1-h_3)\} \times \{(1-h_1)(1-h_2)(1-h_3)h_4\} \\
& \times \{(1-h_1)(1-h_2)(1-h_3)(1-h_4)h_5\} \\
& \times \{(1-h_1)(1-h_2)(1-h_3)(1-h_4)(1-h_5)h_6\}^2 \\
& \times \{(1-h_1)(1-h_2)(1-h_3)(1-h_4)(1-h_5)(1-h_6)(1-h_7)\} \\
=& h_1^2(1-h_1)^8 \times (1-h_2)^8 \times h_3(1-h_3)^6 \\
& h_4(1-h_4)^4 \times h_5(1-h_5)^3 \times h_6^2(1-h_6) \times (1-h_7)
\end{aligned}
$$

# KM estimation

- The likelihood function

$$L(F) = \prod_j h_j^{d_j} (1 - h_j)^{Y(v_j) - d_j}$$

where

$$d_j = \sum_{i=1}^{n} \delta_i I(U_i = v_j) = \#\text{failures at } v_j$$

$$Y(v_j) = \sum_{i=1}^{n} I(U_i \geq v_j) = \#\text{“at risk” at } v_j.$$

# KM estimation

- $\hat{h}_j = d_j / Y(v_j)$

- $$\hat{S}(t) = \begin{cases} 1 & t < v_1 \\ \prod_{i=1}^{j} (1 - \hat{h}_i) & v_j \leq t < v_{j+1} \end{cases},$$

  which is the Kaplan-Meier Estimator.

# Example

| $v_j$ | $Y(v_j)$ | $d_j$ | $\hat{h}_j$ | $\hat{S}(v_j) = \prod_{i=1}^{j}(1-\hat{h}_i) = \hat{P}(T > v_j)$ |
|---|---|---|---|---|
| 2 | 10 | 2 | 2/10 | .8 |
| 5 | 7 | 1 | 1/7 | .69 $(= .8 \times \frac{6}{7})$ |
| 7 | 5 | 1 | 1/5 | .55 $(= .69 \times \frac{4}{5})$ |
| 9 | 4 | 1 | 1/4 | .41 $(= .55 \times \frac{3}{4})$ |
| 16 | 3 | 2 | 2/3 | .14 $(= .41 \times \frac{1}{3})$ |
| 18 | 1 | 0 | 0 | .14 |

# KM estimation

- Suppose that $v_g$ denotes the largest $v_j$ for which $Y(v_j) > 0$.
  1. if $d_g = Y(v_j)$, then $\hat{S}(t) = 0$ for $t \geq v_g$
  2. if $d_g < Y(v_j)$, then $\hat{S}(t) > 0$ but not defined for $t > v_g$. (Not identifiable beyond $v_g$.)
- The survival distribution may not be estimable with right-censored data. Implicit extrapolation is sometimes used.
- The KM estimator can also be used to estimate the survival function for the censoring distribution.

# KM estimation

- KM estimator is a special MLE

$$1 - \hat{S}(t) = \text{argmax}_F L(F)$$

where $F$ is the CDF for all discrete random variables (nonparametric MLE).

# Self-Consistency

- No censoring $\hat{S}(t) = n^{-1} \sum_{i=1}^{n} I(T_i > t)$
- Right censoring: $\hat{S}(t) = n^{-1} \sum_{i=1}^{n} E(I(T_i > t)|U_i, \delta_i)$
  1. $E(I(T_i > t)|U_i, \delta_i = 1) = I(U_i > t)$
  2. $E(I(T_i > t)|U_i, \delta_i = 0) = S(t)/S(U_i) I(t \geq U_i) + I(U_i > t)$
- Self-consistency iteration:

$$\hat{S}_{new}(t) = n^{-1} \sum_{i=1}^{n} \left\{ I(U_i > t) + (1 - \delta_i) \frac{\hat{S}_{old}(t)}{\hat{S}_{old}(U_i)} I(U_i \leq t) \right\}$$

- The solution is still the KM estimator.

# Redistribution of Mass

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Step 1 | $\underline{2}$ | $\underline{2}$ | $\underline{3^+}$ | $\underline{5}$ | $\underline{5^+}$ | $\underline{7}$ | $\underline{9}$ | $\underline{16}$ | $\underline{16}$ | $\underline{18^+}$ |
| Step 2 | $\frac{1}{10}$ | $\frac{1}{10}$ | $\frac{1}{10}$ | $\frac{1}{10}$ | $\frac{1}{10}$ | $\frac{1}{10}$ | $\frac{1}{10}$ | $\frac{1}{10}$ | $\frac{1}{10}$ | $\frac{1}{10}$ |
| Step 3 | $\downarrow$ | $\downarrow$ | $\hookrightarrow$ | $\frac{1}{70}$ | $\frac{1}{70}$ | $\frac{1}{70}$ | $\frac{1}{70}$ | $\frac{1}{70}$ | $\frac{1}{70}$ | $\frac{1}{70}$ |
| | $\downarrow$ | $\downarrow$ | | $\downarrow$ | $\hookrightarrow$ | $\frac{1}{5}\left(\frac{8}{70}\right)$ | $\frac{1}{5}\left(\frac{8}{70}\right)$ | $\frac{1}{5}\left(\frac{8}{70}\right)$ | $\frac{1}{5}\left(\frac{8}{70}\right)$ | $\frac{1}{5}\left(\frac{8}{70}\right)$ |
| Total Mass | $\frac{2}{10}$ | | 0 | $\frac{8}{70}$ | 0 | $\frac{24}{175}$ | $\frac{24}{175}$ | $\frac{48}{175}$ | | Assume this is somewhere $> 18$ |

# Nelson-Aalen Estimator

- How to estimate the cumulative hazard function?

$$\hat{H}(t) = \sum_{i=1}^{j} \hat{h}_i \quad \text{for } v_j \leq t < v_{j+1}$$

- $H(t) = -\log\{S(t)\}$

$$-\log\{\hat{S}(t)\} = \sum_{i=1}^{j} \{-\log(1 - \hat{h}_i)\} \approx \sum_{i=1}^{j} \hat{h}_i = \hat{H}(t)$$

for $v_j \leq t < v_{j+1}$.

## Asymptotical properties of KM estimator

- As $n \to \infty$, $\hat{S}(t) \to S(t)$ in probability.
- As $n \to \infty$, $n^{1/2}\{\hat{S}(t) - S(t)\}$ converges to $N(0, \sigma^2(t))$ in distribution.

# Asymptotical properties of KM estimator

- How to estimate the variance of $\hat{S}(t)$
- $\hat{h}_i$ is an estimated probability.
- The variance of $\hat{h}_i$ can be approximated by

$$\frac{\hat{h}_i(1-\hat{h}_i)}{Y(v_i)} = \frac{d_i(Y(v_i)-d_i)}{Y(v_i)^3}$$

- $\hat{h}_i$ and $\hat{h}_j$ are asymptotically independent (why?).

# Asymptotical variance of KM estimator

$$\text{For } \; v_j \le t < v_{j+1} \; : \; \mathrm{Var}\left(\ln \hat{S}(t)\right) \approx \sum_{i=1}^{j} \mathrm{Var}\left(\ln(1-\hat{h}_i)\right)$$

$$\overset{\delta-\text{method}}{=} \sum_{i=1}^{j} \mathrm{Var}\left(\hat{h}_i\right) \cdot \frac{1}{(1-\hat{h}_i)^2}$$

$$= \sum_{i=1}^{j} \frac{d_i}{Y(v_i)(Y(v_i)-d_i)}.$$

# Asymptotical variance of KM estimator

Using the $\delta$-method

$$
\begin{aligned}
\mathrm{Var}\left(\hat{S}(t)\right) &\approx \mathrm{Var}\left(\ln\hat{S}(t)\right)\left(e^{\ln\hat{S}(t)}\right)^2 \\
&= \hat{S}(t)^2\mathrm{Var}\left(\ln\hat{S}(t)\right) \\
&\approx \hat{S}(t)^2\sum_{i=1}^{j}\frac{d_i}{Y(v_i)(Y(v_i)-d_i)} \quad (v_j \le t < v_{j+1}) \\
&= \hat{\sigma}^2(t)
\end{aligned}
$$

Greenwood's formula

# By-Product

The by-product of the Greenwood's formula is the variance estimator for Nelson-Aalen Estimator:

$$\mathrm{var}(\hat{H}(t)) = \sum_{i=1}^{j} \frac{d_i}{Y(v_i)(Y(v_i) - d_i)}, \quad v_j \leq t < v_{j+1}$$

# Confidence Interval

- $\hat{S}(t) \pm 1.96\hat{\sigma}(t)$, drawbacks?

- By $\delta$-method

$$\mathrm{var}(\log(-\log(\hat{S}(t)))) = \frac{\hat{\sigma}^2(t)}{(\log(\hat{S}(t)))^2 \hat{S}(t)^2}$$

- The confidence interval for $\hat{S}(t)$

$$\left[\exp\{-e^{\log(-\log(\hat{S}(t)))-\frac{1.\hat{9}6\sigma(t)}{\log(\hat{S}(t))\hat{S}(t)}}\}, \exp\{-e^{\log(-\log(\hat{S}(t)))+\frac{1.96\hat{\sigma}(t)}{\log(\hat{S}(t))\hat{S}(t)}}\}\right]$$

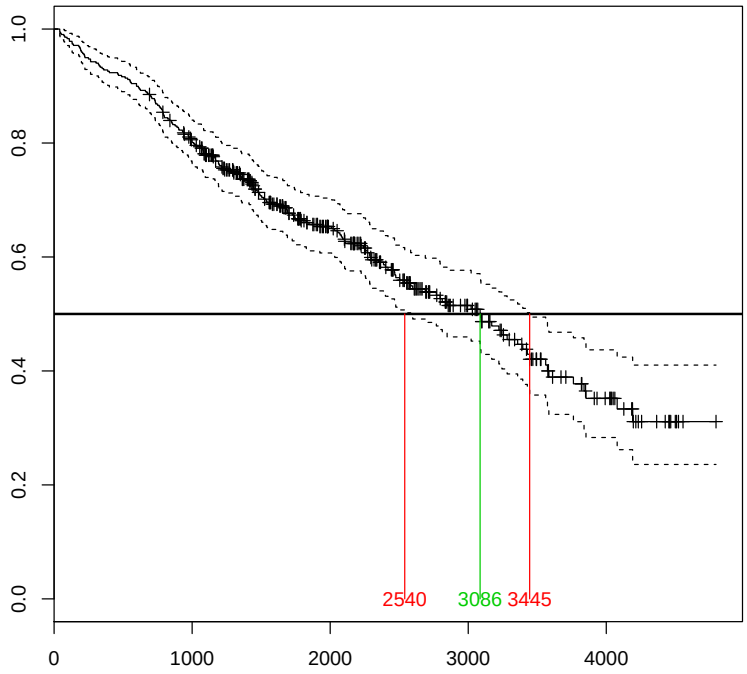
# Median survival time

- How to estimate the median survival time

- Solving $\hat{S}(\hat{t}_M) = 1/2$, not always solvable!

- How to construct the CI for the median survival time?
  Suppose that
  1. $\text{pr}(\hat{S}_L(t) < S(t)) = \text{pr}(\hat{S}_U(t) > S(t)) = 0.975.$
  2. $\hat{S}_L(\hat{t}_{ML}) = 0.5$
  3. $\hat{S}_U(\hat{t}_{MU}) = 0.5$
  4. The confidence interval for $t_M$ is $[\hat{t}_{ML}, \hat{t}_{MU}]$.

# CI for median survival time



# Median survival time

$$0.975 = \mathrm{pr}(\hat{S}_L(t_M) < S(t_M)) = \mathrm{pr}(\hat{S}_L(t_M) < 0.5)$$
$$= \mathrm{pr}(\hat{S}_L(t_M) < \hat{S}_L(\hat{t}_{ML})) = \mathrm{pr}(t_M \geq \hat{t}_{ML})$$

$$0.975 = \mathrm{pr}(\hat{S}_U(t_M) > S(t_M)) = \mathrm{pr}(\hat{S}_U(t_M) > 0.5)$$
$$= \mathrm{pr}(\hat{S}_U(t_M) > \hat{S}_U(\hat{t}_{MU})) = \mathrm{pr}(t_M \leq \hat{t}_{MU})$$

# Restricted mean survival time

- The area under the survival curve is a nice summary for the curve
- The AUC $\mu = \int_0^\tau S(t)dt$ :

$$\mu = tS(t)\Big|_0^\tau + \int_0^\tau tf(t)dt$$

$$= \tau S(\tau) + \int_0^\tau tf(t)dt = \int_0^\infty \min(t,\tau)f(t)dt = E\{\min(t,\tau)\}$$

- $\mu$ can be estimated as

$$\int_0^\tau \hat{S}(t)dt.$$

# Restricted mean survival time

- The restricted mean survival time $E\{\min(T,\tau)\}$ can also be estimated as

$$\hat{\mu}_{IPW} = n^{-1}\sum_{i=1}^{n}\frac{\delta_i + (1-\delta_i)I(U_i \geq \tau)}{\widehat{S}_C(T_i \wedge \tau)}T_i \wedge \tau,$$

  where $\widehat{S}_C(\cdot)$ is a consistent estimator of the survival function of the censoring time $C$. (How?)

- Rational

$$E\left[\frac{I(C_i \geq \tau \wedge T_i)}{\widehat{S}_C(T_i \wedge \tau)}T_i \wedge \tau | T_i\right] \approx (T_i \wedge \tau)\frac{P(C_i \geq \tau \wedge T_i | T_i)}{S_C(T_i \wedge \tau)} = T_i \wedge \tau$$

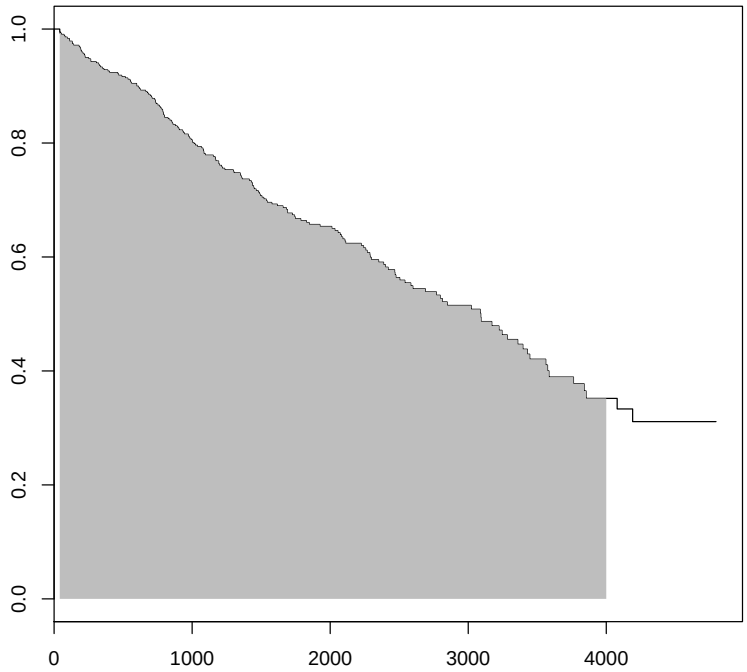
- This type of estimator is called the inverse probability weighting estimator

# Restricted mean survival time

- $\hat{\mu}$ and $\hat{\mu}_{IPW}$ are equivalent!
- The variance of the estimated area under the survival curve is complicated (the derivation will be given later).

$$\frac{1}{n}\int_0^\tau \frac{\left\{\int_t^\tau S(u)du\right\}^2 h(t)dt}{P(U \geq t)}.$$

# Area under the KM curve

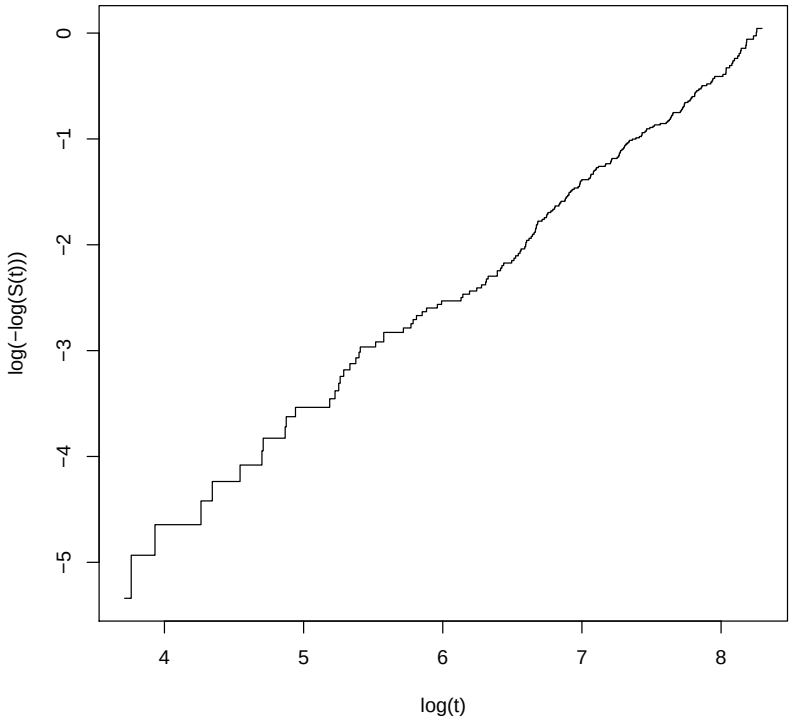


# Model Checking

- Under the exponential distribution: $\log(S(t)) = -\lambda t$
- Plot $t$ vs. $\log(\hat{S}(t))$ to visually check the expected linear pattern.
- Under the Weibull distribution
  $\log(-\log(S(t))) = p\log(\lambda) + p\log(t)$

- Plot $\log(t)$ vs. $\log(-\log(\hat{S}(t)))$ to visually check the expected linear pattern.

# Model Checking



**Coming Soon**

- The distribution of $\hat{S}(t)$ as a process.