Estimation with Event-Time Data

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The Kaplan-Meier estimator

Approaches to estimating $S(t)$

- Parametric models and maximum likelihood
- *The non-parametric Kaplan-Meier (KM) estimate*
  - KM also called the product limit estimator because of original derivation

The Kaplan-Meier Estimator: General idea

The Kaplan-Meier estimator is probably the most popular approach.

When there is no censoring, the general formula is:

$$\widehat{S}(t) = \frac{\#\ \textit{individuals with}\ T > t}{\textit{total sample size}}$$

An example: Cox and Oakes, no censoring

Time to relapse (weeks) for 21 leukemia patients receiving control treatment[1]:

- 1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

What is $\widehat{S}(10) = \widehat{P}(T > 10)$, the probability that an individual survives more than 10 weeks?

- This is $8/21 = 0.38$ since 8 people survive more than 10 weeks.

What about $\widehat{S}(8)$?

- $\widehat{S}(8) = \widehat{P}(T > 8) = 8/21 = 0.38$
- The four events at $t = 8$ are counted as having already failed.

[1] Table 1.1 of Cox & Oakes, 1984

Empirical survival function

When there is no censoring, the general formula is:

$$\widehat{S}(t) = \frac{\#\ \textit{individuals with}\ T > t}{\textit{total sample size}}$$

What is the standard error of $\widehat{S}(t)$?

- When there is no censoring, the estimated survival function is a proportion $\hat{p}$ with the standard error:

$$\text{s.e.}[\widehat{S}(t)] = \sqrt{p(1-p)/n}$$

$$\text{Example: s.e.}[\widehat{S}(8)] = \sqrt{(0.38)(0.62)/21} = 0.106$$

A table of $\widehat{S}(t)$

Values of t	# individuals with $T > t$	$\widehat{S}(t)$
$0 \leq t < 1$	21	21/21=1.000
$1 \leq t < 2$	19	19/21=0.905
$2 \leq t < 3$	17	17/21=0.809
$3 \leq t < 4$	16	16/21=0.762
$4 \leq t < 5$	14	14/21=0.667
$5 \leq t < 8$	12	12/21=0.571
$8 \leq t < 11$	8	8/21=0.381
$11 \leq t < 12$	6	6/21=0.286
$12 \leq t < 15$	5	4/21=0.191
$15 \leq t < 17$	3	3/21=0.143
$17 \leq t < 22$	2	2/21=0.095
$22 \leq t < 23$	1	1/21=0.048

What about censoring?

Consider time to relapse (weeks) for leukemia patients in the treatment group.[2] Times with $^+$ are right censored:

$$6^+, 6, 6, 6, 7, 9^+, 10^+, 10, 11^+, 13, 16, 17^+$$

$$19^+, 20^+, 22, 23, 25^+, 32^+, 32^+, 34^+, 35^+$$

Naturally, $\widehat{S}(6-) = 21/21$

- because everyone survived until at least time 6 or greater

Not right to claim $\widehat{S}(6) = 17/21$

- due to unknown status of person censored at time 6

[2] Table 1.1 of Cox and Oakes

Censoring with the Kaplan-Meier

In a 1958 paper in the *Journal of the American Statistical Association*, Kaplan and Meier proposed a way to nonparametrically estimate $S(t)$, in the presence of censoring.

The method is based on the ideas of *conditional probability*.

Censoring and the KM estimator

$S(t)$ in the discrete case:

To estimate $S(t)$ for time t within the interval t_k and t_{k+1}, e.g. $t_k \leq t < t_{k+1}$, consider the intervals defined by the ordered k failure times,

$$[t_0, t_1), [t_1, t_2), \ldots, [t_{k-1}, t_k), [t_k, \infty)$$

The KM estimate is constructed based on events within each interval $[t_j, t_{j+1})$

- d_j is the number of deaths in the interval $[t_j, t_{j+1})$
- r_j is the number of individuals at risk in the interval $[t_j, t_{j+1})$

Initial assumptions: $t_0 = 0, \quad P(T > t_0) = 1.$

Censoring and the KM: discrete case

Then,

$$
\begin{aligned}
S(t) = P(T > t) &= P(T > t_k) \\
&= P(T > t_1, T > t_2, \ldots, T > t_k) \\
&= P(T > t_1) \times \prod_{j=2}^{k} P(T > t_j | T > t_{j-1}) \\
&\overset{(*)}{=} \prod_{j=1}^{k} [1 - P(T = t_j | T > t_{j-1})] = \prod_{j=1}^{k} [1 - \lambda_j]
\end{aligned}
$$

$$
\text{so} \quad \widehat{S}(t) \cong \prod_{j=1}^{k} \left(1 - \frac{d_j}{r_j}\right) = \prod_{j: t_j \leq t} \left(1 - \frac{d_j}{r_j}\right)
$$

(*) Initial assumptions: $t_0 = 0, \;\; P(T > t_0) = 1.$

Censoring and the KM: continuous case

For continuous data, the Kaplan-Meier estimator of the survivorship function $S(t) = P(T > t)$ is

$$\widehat{S}(t) = \prod_{j:\tau_j \leq t} \frac{r_j - d_j}{r_j} = \prod_{j:\tau_j \leq t} \left(1 - \frac{d_j}{r_j}\right), \text{where}$$

- $\tau_1, \ldots, \tau_K$ are the K distinct death times observed
- d_j is the number of deaths at τ_j
- r_j is the number of individuals "at risk" right before the j-th death time (everyone dead or censored *at or after* that time).
  - $r_j = r_{j-1} - d_{j-1} - c_{j-1}$
  - Alternatively, $r_j = \sum_{l \geq j}(c_l + d_l)$
- c_j is the number of censored observations between the j-th and $(j+1)$-th death times.
  - Censorings tied at τ_j are included in c_j

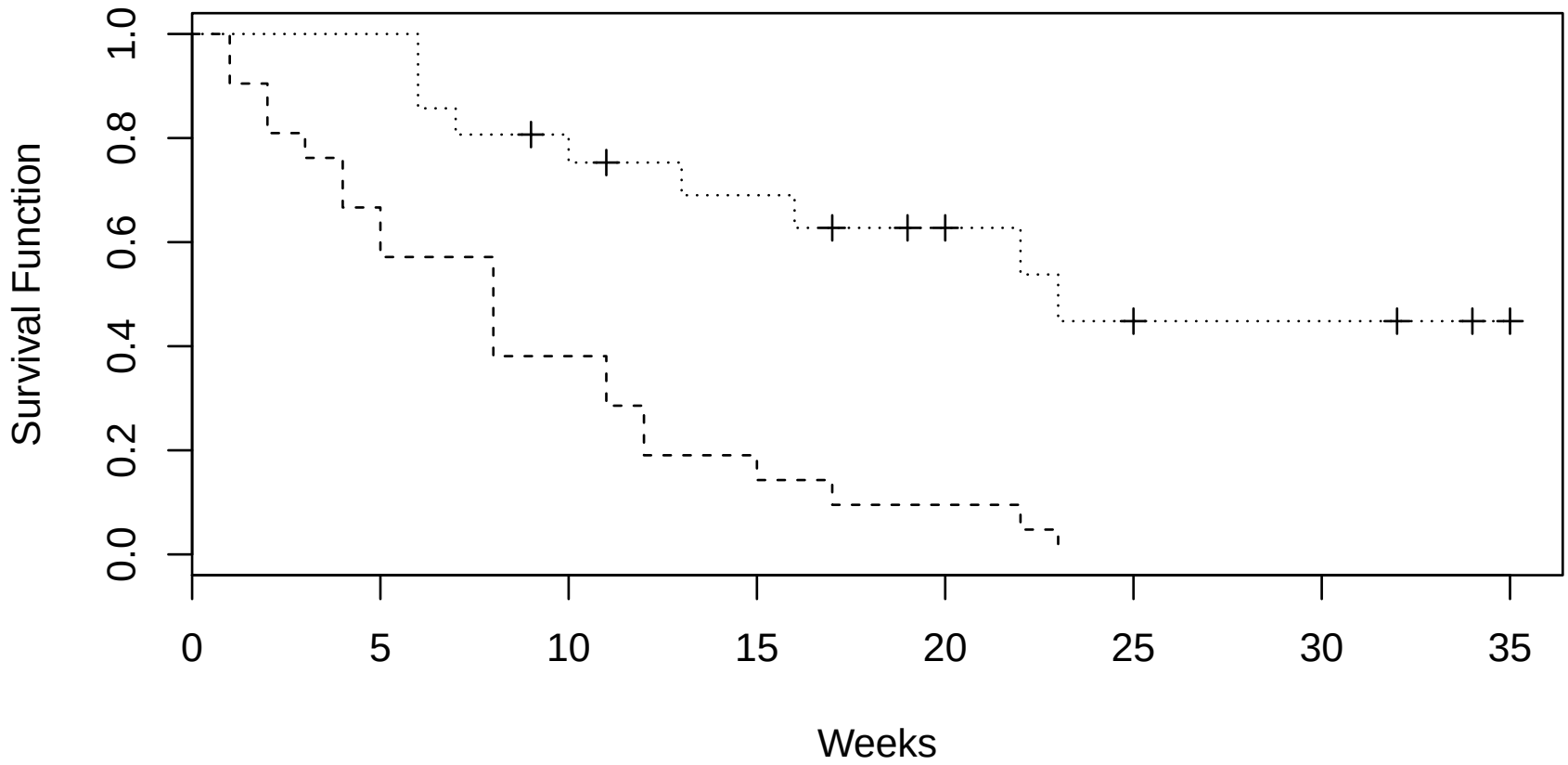
Computing

Most widely used software packages (SAS, Stata, R) have modules for survival analysis.

We will focus on R since it is free and has very good survival routines written by Terry Therneau.

Fitting a Kaplan-Meier in R

```r
library(survival)
library(eventtimedata)
data("cox.oakes.leukemia")
leukemia.remission <- survfit(Surv(time, relapse) ~ group,
                              data = cox.oakes.leukemia)
plot(leukemia.remission, lty = 2:3, mark.time = TRUE, xlab = "Weeks",
     ylab = "Survival Function" )
```



Numerical output

```
library(survival)
library(eventtimedata)
print(leukemia.remission)
```

```
## Call: survfit(formula = Surv(time, relapse) ~ group, data = cox.oake
##
##           n events median 0.95LCL 0.95UCL
## group=0 21     21      8       4      12
## group=1 21      9     23      16      NA
```

KM numerical estimates, group == 0

```
leukemia.group.0 = subset.data.frame(cox.oakes.leukemia, group == 0)
km.group.0 = survfit(Surv(time, relapse) ~ 1, data = leukemia.group.0)

summary(km.group.0)
```

```
## Call: survfit(formula = Surv(time, relapse) ~ 1, data = leukemia.group.0)
##
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##     1     21       2   0.9048  0.0641      0.78754        1.000
##     2     19       2   0.8095  0.0857      0.65785        0.996
##     3     17       1   0.7619  0.0929      0.59988        0.968
##     4     16       2   0.6667  0.1029      0.49268        0.902
##     5     14       2   0.5714  0.1080      0.39455        0.828
##     8     12       4   0.3810  0.1060      0.22085        0.657
##    11      8       2   0.2857  0.0986      0.14529        0.562
##    12      6       2   0.1905  0.0857      0.07887        0.460
##    15      4       1   0.1429  0.0764      0.05011        0.407
##    17      3       1   0.0952  0.0641      0.02549        0.356
##    22      2       1   0.0476  0.0465      0.00703        0.322
##    23      1       1   0.0000     NaN           NA           NA
```

KM numerical estimates, group == 1

```
leukemia.group.1 = subset.data.frame(cox.oakes.leukemia, group == 1)
km.group.1 = survfit(Surv(time, relapse) ~ 1, data = leukemia.group.1)

summary(km.group.1)
```

```
## Call: survfit(formula = Surv(time, relapse) ~ 1, data = leukemia.group.1)
##
##  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
```

Subsets used here only to fit output on slides.

`summary(leukemia.remission)` prints values for both groups.

Estimating standard errors

Pointwise confidence intervals for the KM

Why *pointwise*?

- Since the KM is a function of time, there is an estimate of the standard error (or the variance) at each time.

Greenwood's formula is the most commonly used estimate of the KM standard error.

$$\widehat{\text{var}}(\widehat{S}(t)) = [\widehat{S}(t)]^2 \sum_{j:\tau_j \leq t} \frac{d_j}{(r_j - d_j) r_j}$$

Derivation given later in the slides.

Confidence intervals for the KM

A 95% confidence interval could be based on

$$\widehat{S}(t) \pm z_{1-\alpha/2} \times \text{s.e.}[\widehat{S}(t)],$$

with s.e.$[\widehat{S}(t)]$ estimated using Greenwood's formula.

- However, this approach can yield values > 1 or < 0.

The better approach is to use the *log-log* transformation and base intervals around

$$L(t) = \log[-\log[S(t)]]$$

In R, use the option `conf.type = "log-log"`. The default transformation in R is $L(t) = -\log[S(t)]$.

Confidence intervals . . .

To transform back, use $S(t) = \exp[-\exp[L(t)]]$.

Since. . .

- $0 \leq S(t) \leq 1$,
- $0 \leq -\log[S(t)] < \infty$, and
- $-\infty < \log[-\log[S(t)]] < \infty$,

the confidence interval will be in the proper range when transformed back.

Log-log approach for confidence intervals:

1. Define $L(t) = \log[-\log[S(t)]]$.
2. Form a 95% confidence interval for $L(t)$, $(\widehat{L}(t) - A, \widehat{L}(t) + A)$, with $A = 1.96 \times \text{s.e.}[\widehat{L}(t)]$.
3. Apply $S(t) = \exp[-\exp[L(t)]]$ to obtain the confidence bounds for the 95% CI on $S(t)$,

$$\left(\exp[-e^{(\widehat{L}(t)+A)}], \exp[-e^{(\widehat{L}(t)-A)}]\right)$$

4. Substituting $\widehat{L}(t) = \log[-\log[\widehat{S}(t)]]$ back into the above bounds yields confidence bounds of

$$\left([\widehat{S}(t)]^{e^{A}}, [\widehat{S}(t)]^{e^{-A}}\right)$$

Confidence intervals for median survival

The median is usually defined as

$$q_{0.5} = \min\{t_j : \widehat{S}(t) = 0.5\}.$$

Other quantiles are defined similarly.

Confidence limits for median survival are based on confidence intervals for $S(t)$.

R uses the method due to Brookmeyer and Crowley (Biometrics 1982, 38, 29–41).

- SAS and other packages use this as well.

The formulas are complex and not shown here.

The cumulative hazard estimator

Estimating $S(t)$ via the Nelson-Aalen cumulative hazard

The cumulative hazard $\Lambda(t)$ can be approximated by a sum over j intervals,

$$\Lambda(t) \approx \sum_j \lambda_j \Delta$$

where

- λ_j is the value of the hazard in the j^{th} interval
- Δ is the width of each interval

Since $\widehat{\lambda}_j \Delta$ is approximately the probability of having an event in an interval j, conditional on having survived until the beginning of the interval, $\Lambda(t)$ can be approximated further as

$$\Lambda(t) \approx \sum_j \lambda_j \Delta \approx \sum_j \frac{d_j}{r_j}$$

Estimating $S(t)$ via the Nelson-Aalen cumulative hazard ...

Thus, the *Nelson-Aalen estimator* can be written as

$$\widehat{\Lambda}_{NA}(t) = \sum_{t_j \leq t} \frac{d_j}{r_j}$$

From $\widehat{\Lambda}_{NA}(t)$, an alternative to the KM estimator of $S(t)$ can be calculated:

$$\widehat{S}_{FH}(t) = \exp[-\widehat{\Lambda}_{NA}(t)]$$

The *Fleming-Harrington estimator* is generally very close to $\widehat{S}_{KM}(t)$.

Example: Time to recidivism, Rossi (1980)

Recidivism is the event of rearrest and reincarceration after release from prison.

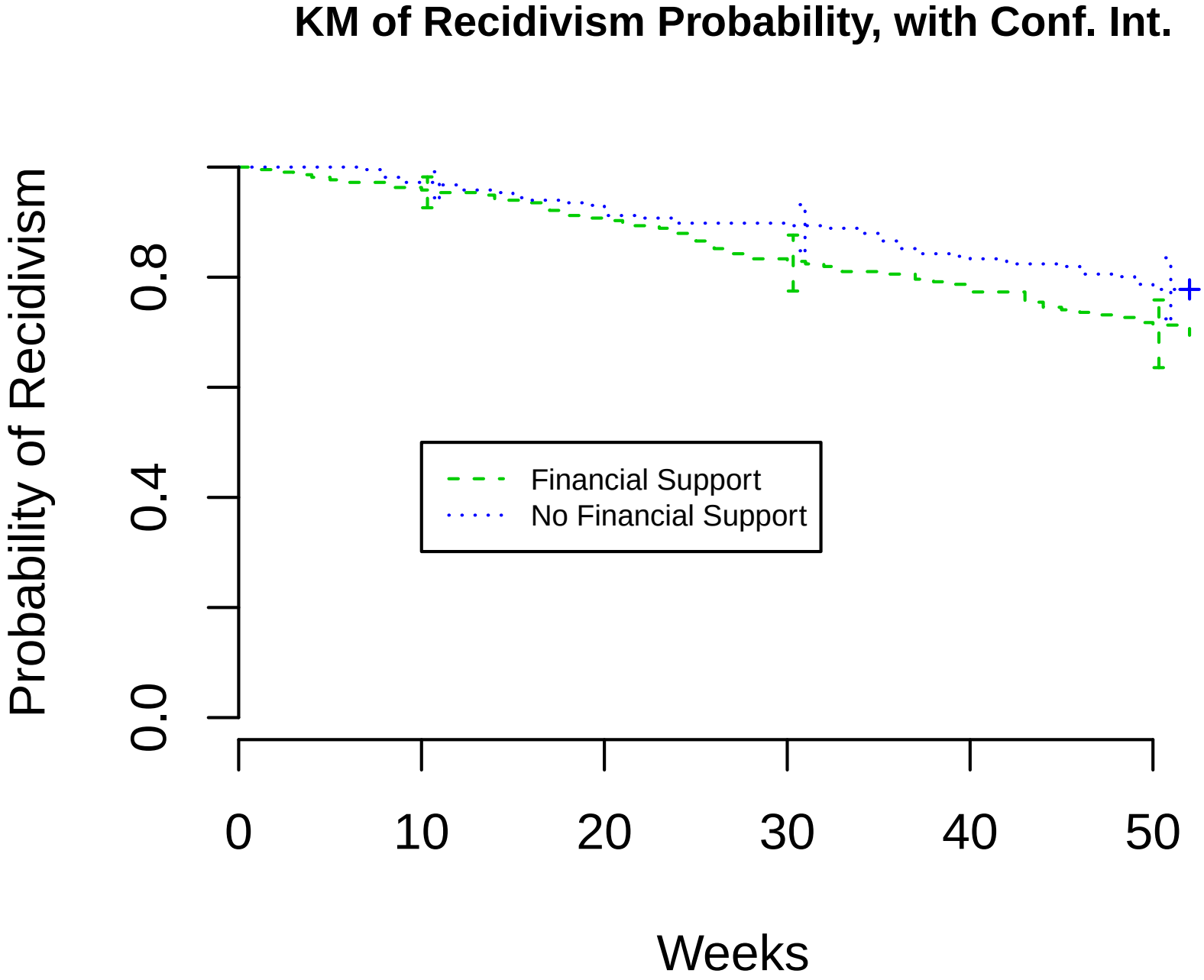
A randomized study[3] with 52 weeks of follow-up after randomization collected information on the following variables:

- `fin`: Financial support vs no financial support after release
- `week`: Time in weeks to either re-arrest or censoring
- `arrest`: 1 = arrest during the follow-up, 0 = no arrest

[3] `rossi` dataset in `eventtimedata` package.

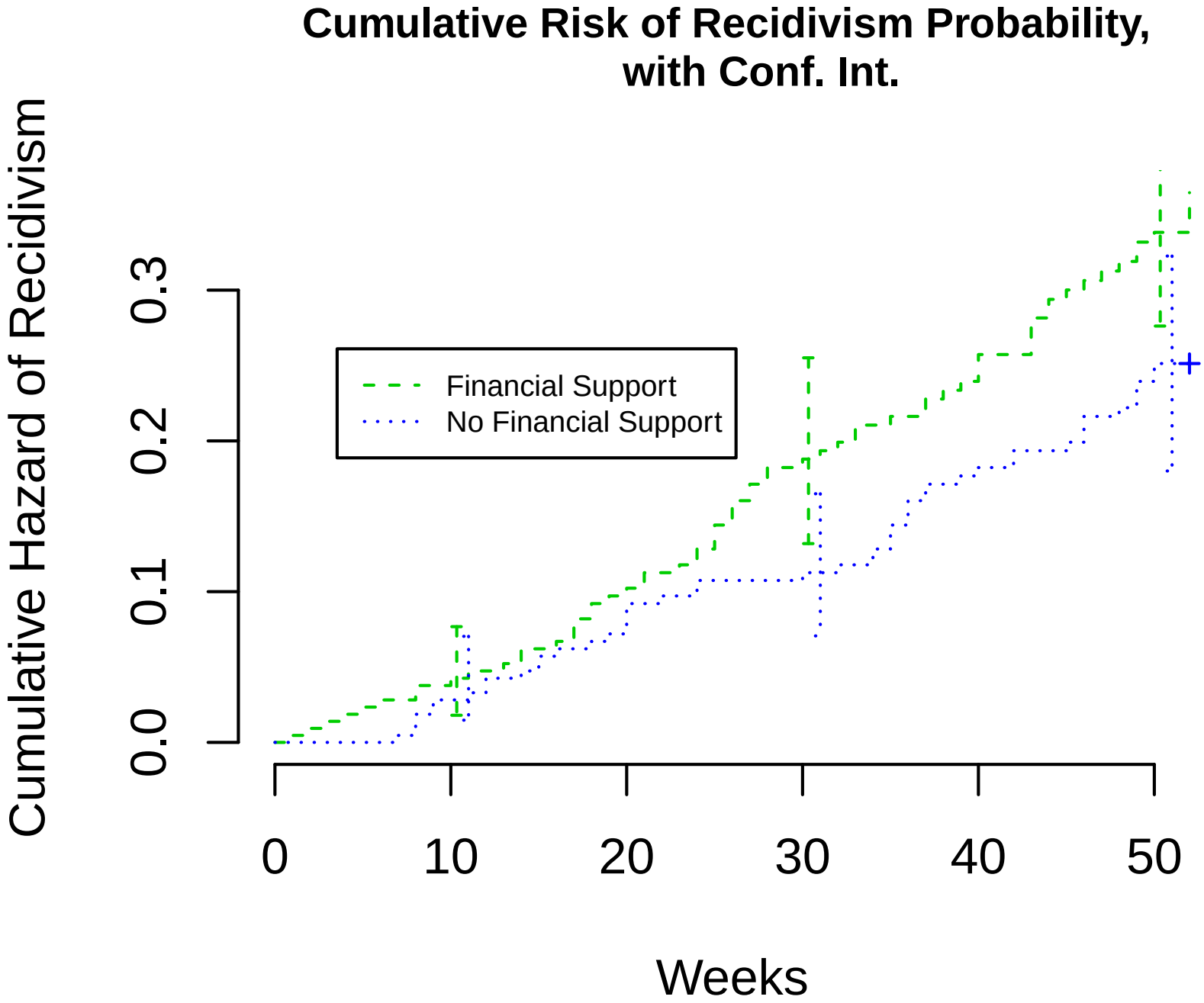
KM of recidivism, with confidence intervals

```
library(survival)
library(eventtimedata)
data("rossi")
rossi.recidivism.km <- survfit(Surv(week, arrest) ~ fin,
                               data = rossi)
plot(rossi.recidivism.km, lty = 2:3, col = 3:4, mark.time = TRUE,
     xlab = "Weeks",
     ylab = "Probability of Recidivism",
     axes = FALSE,
     conf.times = c(10,30,50),
     main = "KM of Recidivism Probability, with Conf. Int.",
     cex = 0.6, cex.main = 0.8)
axis(1)
axis(2)
legend(10, .5, c("Financial Support", "No Financial Support"),
       lty = 2:3, col = 3:4, cex = 0.6)
```


KM of Recidivism Probability, with Conf. Int.
Probability of Recidivism
0.0
0.4
0.8
Financial Support
No Financial Support
0
10
20
30
40
50
Weeks

Cumulative hazard (risk) of recidivism, w/CIs

```
library(survival)
library(eventtimedata)
data("rossi")
rossi.recidivism.ch <- survfit(Surv(week, arrest) ~ fin,
                               data = rossi)
plot(rossi.recidivism.km, lty = 2:3, col = 3:4, mark.time = TRUE,
     fun = "cumhaz",
     xlab = "Weeks",
     ylab = "Cumulative Hazard of Recidivism",
     axes = FALSE,
     conf.times = c(10,30,50),
     main = "Cumulative Risk of Recidivism Probability,
     with Conf. Int.",
     cex = 0.6, cex.main = 0.8)
axis(1)
axis(2)
legend("topleft", inset = c(0.1, 0.3),
       c("Financial Support", "No Financial Support"),
       lty = 2:3, col = 3:4, cex = 0.6)
```


Cumulative Risk of Recidivism Probability,
with Conf. Int.
Cumulative Hazard of Recidivism
0.0
0.1
0.2
0.3
Financial Support
No Financial Support
0
10
20
30
40
50
Weeks

Confidence intervals vs confidence bands

Examining many confidence intervals may cause the same problem as simultaneous hypothesis tests.

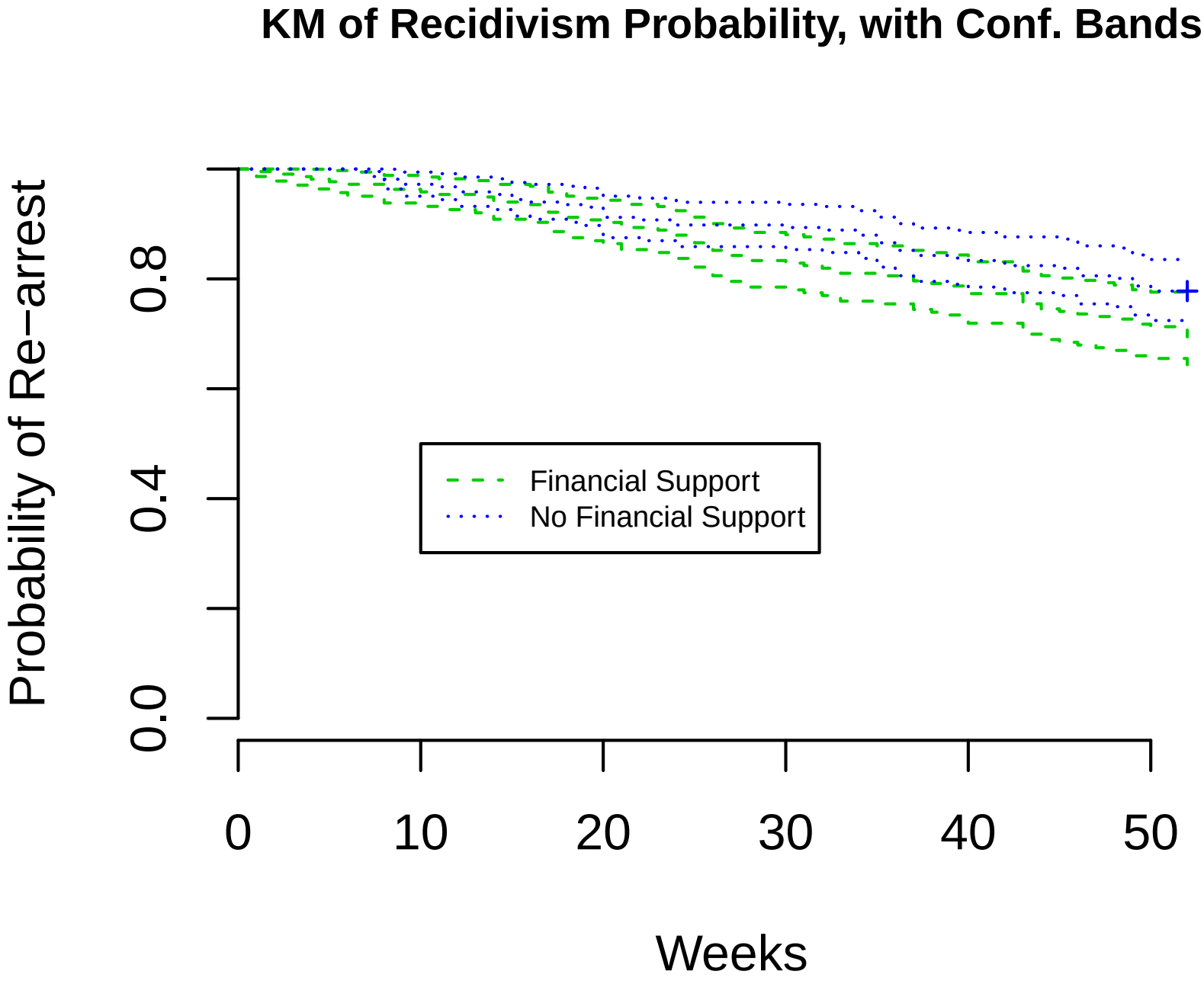
- Overall coverage probability for the curve is not right.

Hall and Wellner (*Biometrika*, 1980) solved that problem by deriving confidence bands:

- 95% bands have probability 0.95 of covering the entire survival curve.
- These bands will be wider than pointwise intervals.
- Formulas complex, not shown here.

KM of recidivism, with confidence bands

```
library(survival)
library(eventtimedata)
data("rossi")
rossi.recidivism.km <- survfit(Surv(week, arrest) ~ fin,
                               data = rossi)
plot(rossi.recidivism.km, lty = 2:3, col = 3:4, mark.time = TRUE,
     xlab = "Weeks",
     ylab = "Probability of Re-arrest",
     axes = FALSE,
     conf.int = TRUE,
     main = "KM of Recidivism Probability, with Conf. Bands",
     cex = 0.6, cex.main = 0.8)
axis(1)
axis(2)
legend(10, .5, c("Financial Support", "No Financial Support"),
       lty = 2:3, col = 3:4, cex = 0.6)
```


KM of Recidivism Probability, with Conf. Bands
Probability of Re−arrest
0.0
0.4
0.8
0
10
20
30
40
50
Weeks
Financial Support
No Financial Support

Example: Application to FDA (7 March 2018)

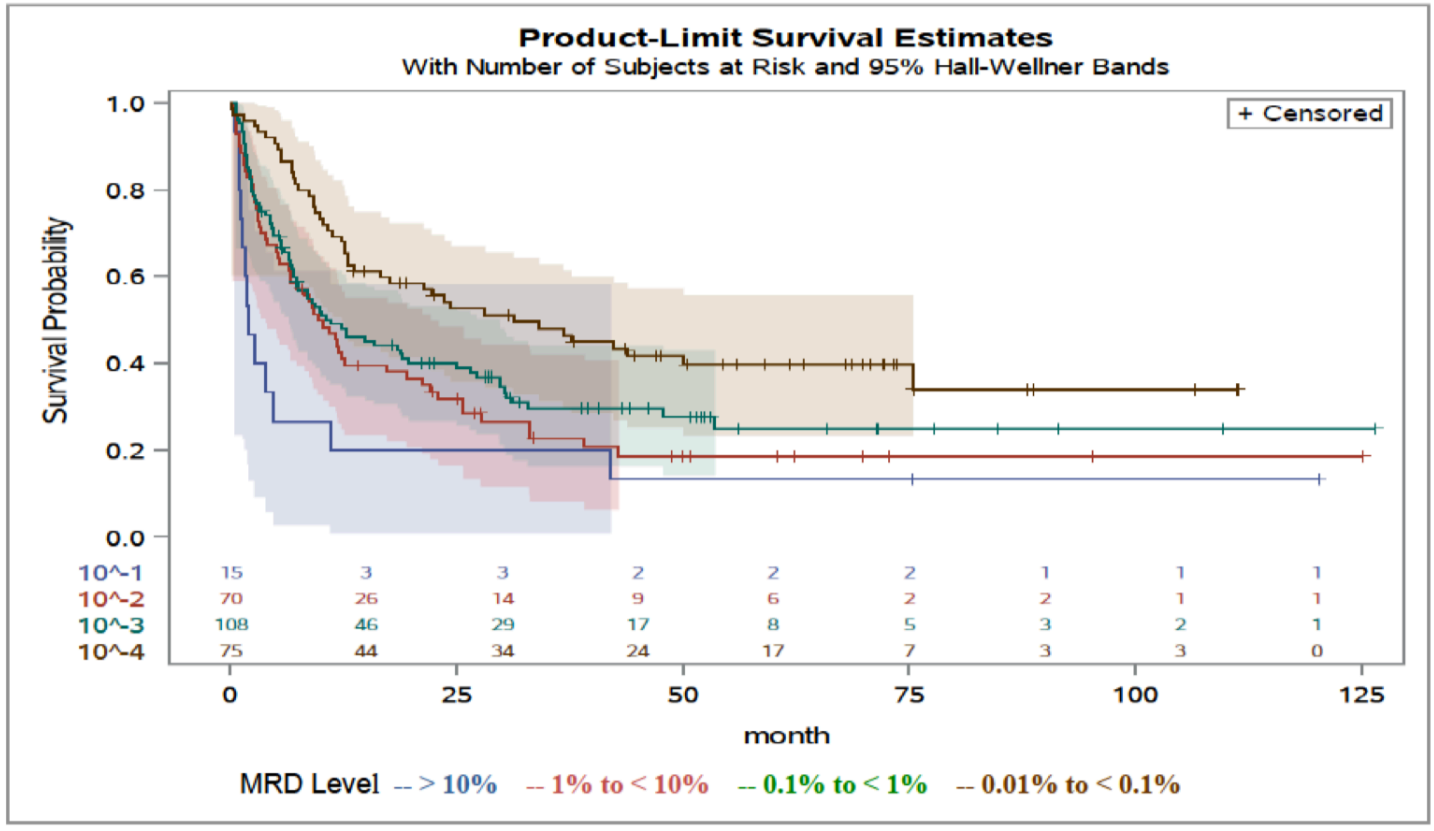
On 7 March 2018, Amgen asked for FDA approval of the drug blinatumumab in patients with a sub-type of acute lymphoblastic leukemia (ALL).

- The drug would be given to patients who experienced a clinical complete remission, but had evidence of minimal residual disease (MRD).

Figure on the next slide from the FDA analysis of the data shows

- Relapse free survival by MRD status
- Shows confidence bands (Hall and Wellner)

Figure 1: Study 20120148 - Kaplan-Meier Plot of Hematological RFS of Patients by Baseline MRD Level



Source: FDA analysis

Figure 1: FDA presentation, 7 March 2018

Derivations

KM estimator derivation, continuous case ...

Conditional Probability: Suppose A and B are two events. Then,

$$P(A|B) = \frac{P(A \cap B)}{P(B)}$$

Multiplication Law: Multiply both sides of the above by $P(B)$.

$$P(A \cap B) = P(A|B)P(B)$$

Extension to more than 2 events: Suppose $A_1, A_2, \ldots, A_k$ are k different events. Then, the probability of all k events occurring can be written as a product of conditional probabilities.

$$\begin{aligned} P(A_1 \cap A_2 \ldots \cap A_k) = P(A_k|A_{k-1} \cap \ldots \cap A_1) \\ \times P(A_{k-1}|A_{k-2} \cap \ldots \cap A_1) \\ \times \ldots \\ \times P(A_2|A_1) \\ \times P(A_1) \end{aligned}$$

KM estimator derivation, continuous case . . .

Think of dividing the observed time-span of the study into a series of small intervals so that there is a separate interval for each time of death or censoring (with possible ties):

Using the law of conditional probability,

$$P(T > t) = \prod_j P(\text{survive } j\text{-th interval } I_j \mid \text{survived to start of } I_j),$$

over all intervals preceding time t.

KM estimator derivation, continuous case . . .

Four possibilities for each interval:

1. No event: conditional probability of surviving the interval is 1.
2. Censoring: assume individual survives to end of the interval, so that the conditional probability of surviving the interval is 1.
3. Death, but no censoring: conditional probability of *not* surviving the interval is # deaths (d) divided by # "at risk" (r) at the beginning of the interval. Thus, the conditional probability of surviving the interval is $1 - \frac{d}{r}$.
4. Tied deaths and censoring: assume censorings survive to end of the interval, so that conditional probability of surviving the interval is still $1 - \frac{d}{r}$.

Thus, the general formula for the conditional probability of surviving the j-th interval that holds for all 4 cases is $1 - \frac{d_j}{r_j}$.

KM estimator derivation, continuous case ...

As the intervals become smaller,

- The approximations made in estimating the probabilities of surviving each interval become smaller.
- The estimator converges to the true $S(t)$ as the sample size increases.

This argument clarifies why an alternative name for the KM is the *product limit estimator*.

Result stated earlier

For continuous data, the Kaplan-Meier estimator of the survivorship function $S(t) = P(T > t)$ is

$$\widehat{S}(t) = \prod_{j:\tau_j \leq t} \frac{r_j - d_j}{r_j} = \prod_{j:\tau_j \leq t} \left(1 - \frac{d_j}{r_j}\right), \text{where}$$

- $\tau_1, \ldots, \tau_K$ are the K distinct death times observed
- d_j is the number of deaths at τ_j
- r_j is the number of individuals "at risk" right before the j-th death time (everyone dead or censored *at or after* that time).
  - $r_j = r_{j-1} - d_{j-1} - c_{j-1}$
  - Alternatively, $r_j = \sum_{l \geq j}(c_l + d_l)$
- c_j is the number of censored observations between the j-th and $(j+1)$-th death times.
  - Censorings tied at τ_j are included in c_j

Derivation of Greenwood's formula

KM estimator can be thought of as

$$\widehat{S}(t) = \prod_{j:\tau_j \leq t} (1 - \widehat{\lambda}_j), \text{ where } \widehat{\lambda}_j = \frac{d_j}{r_j}.$$

Since the $\widehat{\lambda}_j$'s are (conditionally) binomial proportions, standard likelihood theory can be used to to show each $\widehat{\lambda}_j$ is approximately normally distributed, with mean λ_j, and variance[4]

$$\text{var}(\widehat{\lambda}_j) = \frac{\lambda_j(1-\lambda_j)}{r_j}$$

The $\widehat{\lambda}_j$'s are independent in large enough samples.

[4] The estimated variance is $\widehat{\text{var}}(\widehat{\lambda}_j) = \frac{\widehat{\lambda}_j(1-\widehat{\lambda}_j)}{r_j}$.

Derivation of Greenwood's formula ...

Since $\widehat{S}(t)$ is a function of the λ_j's, its variance can be estimated using the *delta method*,

- an approach for calculating the variance of non-linear functions.

Delta method: If Y is normal with mean μ and variance σ^2, then $g(Y)$ is approximately normally distributed with mean $g(\mu)$ and variance $[g'(\mu)]^2\sigma^2$.

Digression: the delta method

Two specific examples that will be used in the derivation:

- Ex. 1: $Z = g(Y) = \log(Y)$, then $g'(y) = (1/y)$:

$$Z \sim N\left(\log(\mu), \left(\frac{1}{\mu}\right)^2 \sigma^2\right)$$

- Ex. 2: $Z = g(Y) = \exp(Y)$, then $g'(y) = e^y$:

$$Z \sim N\left(e^{\mu}, [e^{\mu}]^2 \sigma^2\right)$$

Derivation of Greenwood's formula ...

Instead of dealing with $\widehat{S}(t)$ directly, use $\log[\widehat{S}(t)]$ since calculating variance of a sum is easier than calculating variance of a product,

$$\log[\widehat{S}(t)] = \sum_{j:\tau_j \le t} \log(1 - \widehat{\lambda}_j)$$

By approximate independence of the $\widehat{\lambda}_j$'s,

$$\text{var}(\log[\widehat{S}(t)]) = \sum_{j:\tau_j \le t} \text{var}[\log(1 - \widehat{\lambda}_j)].$$

Apply the delta method (Ex. 1), where $\mu = 1 - \lambda_j$ and $\sigma^2 = \frac{\lambda_j(1-\lambda_j)}{r_j}$.

$$\begin{aligned}
\widehat{\text{var}}(\log[\widehat{S}(t)]) &= \sum_{j:\tau_j \le t} \left(\frac{1}{1 - \widehat{\lambda}_j}\right)^2 \left(\frac{\widehat{\lambda}_j(1 - \widehat{\lambda}_j)}{r_j}\right) \\
&= \sum_{j:\tau_j \le t} \frac{\widehat{\lambda}_j}{(1 - \widehat{\lambda}_j) r_j} = \sum_{j:\tau_j \le t} \frac{d_j}{(r_j - d_j) r_j}
\end{aligned}$$

Greenwood's formula

To obtain $\widehat{\text{var}}(\widehat{S}(t))$, apply the delta method again (Ex. 2), using the relationship $\widehat{S}(t) = \exp[\log[\widehat{S}(t)]]$,

$$\widehat{\text{var}}(\widehat{S}(t)) = [\widehat{S}(t)]^2 \, \widehat{\text{var}}\left[\log[\widehat{S}(t)]\right]$$

Substitute the previous result for $\widehat{\text{var}}\left[\log[\widehat{S}(t)]\right]$ to obtain Greenwood's Formula,

$$\widehat{\text{var}}(\widehat{S}(t)) = [\widehat{S}(t)]^2 \sum_{j:\tau_j \leq t} \frac{d_j}{(r_j - d_j) r_j}$$