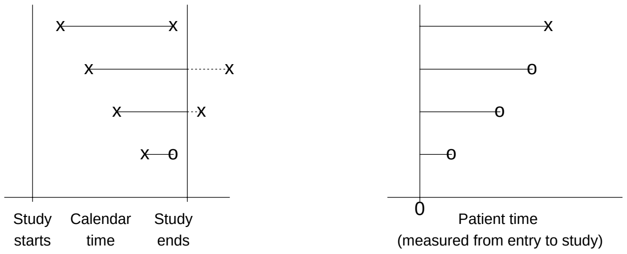
2 Right Censoring and Kaplan-Meier Estimator

In biomedical applications, especially in clinical trials, two important issues arise when studying "time to event" data (we will assume the event to be "death". It can be any event of interest):

1. Some individuals are still alive at the end of the study or analysis so the event of interest, namely death, has not occurred. Therefore we have right censored data.
2. Length of follow-up varies due to staggered entry. So we cannot observe the event for those individuals with insufficient follow-up time.

Note: It is important to distinguish calendar time and patient time

Figure 2.1: *Illustration of censored data*



In addition to censoring because of insufficient follow-up (*i.e.*, end of study censoring due to staggered entry), other reasons for censoring includes

- loss to follow-up: patients stop coming to clinic or move away.
- deaths from other causes: competing risks.

Censoring from these types of causes may be inherently different from censoring due to staggered entry. We will discuss this in more detail later.

Censoring and differential follow-up create certain difficulties in the analysis for such data as is illustrated by the following example taken from a clinical trial of 146 patients treated after they had a myocardial infarction (MI).

The data have been grouped into one year intervals and all time is measured in terms of patient time.

Table 2.1: *Data from a clinical trial on myocardial infarction (MI)*

Year since entry into study	Number alive and under observation at beginning of interval	Number dying during interval	Number censored or withdrawn
$[0, 1)$	146	27	3
$[1, 2)$	116	18	10
$[2, 3)$	88	21	10
$[3, 4)$	57	9	3
$[4, 5)$	45	1	3
$[5, 6)$	41	2	11
$[6, 7)$	28	3	5
$[7, 8)$	20	1	8
$[8, 9)$	11	2	1
$[9, 10)$	8	2	6

Question: Estimate the 5 year survival rate, *i.e.*, $S(5) = P[T \geq 5]$.

Two naive and incorrect answers are given by

1. $\widehat{F}(5) = P[T < 5] = \dfrac{\text{76 deaths in 5 years}}{\text{146 individuals}} = 52.1\%$, $\widehat{S}(5) = 1 - \widehat{F}(5) = 47.9\%$.
2. $\widehat{F}(5) = P[T < 5] = \dfrac{\text{76 deaths in 5 years}}{\text{146 -29 (withdrawn in 5 years)}} = 65\%$, $\widehat{S}(5) = 1 - \widehat{F}(5) = 35\%$.

Obviously, we can observe the following

1. The first estimate would be correct if all censoring occurred after 5 years. Of cause, this was not the case leading to overly **optimistic** estimate (*i.e.*, overestimates $S(5)$).

2. The second estimate would be correct if all individuals censored in the 5 years were censored immediately upon entering the study. This was not the case either, leading to overly **pessimistic** estimate (*i.e.*, underestimates $S(5)$).

Our clinical colleagues have suggested eliminating all individuals who are censored and use the remaining "complete" data. This would lead to the following estimate

$$\widehat{F}(5) = P[T \leq 5] = \frac{\text{76 deaths in 5 years}}{\text{146 -60 (censored)}} = 88.4\%, \quad \widehat{S}(5) = 1 - \widehat{F}(5) = 11.6\%.$$

This is even **more pessimistic** than the estimate given by (2).

Life-table Estimate

More appropriate methods use **life-table** or **actuarial** method. The problem with the above two estimates is that they both ignore the fact that each one-year interval experienced censoring (or withdrawing). Obviously we need to take this information into account in order to reduce bias. If we can express $S(5)$ as a function of quantities related to each interval and get a very good estimate for each quantity, then intuitively, we will get a very good estimate of $S(5)$. By the definition of $S(5)$, we have:

$$\begin{aligned}
S(5) &= P[T \geq 5] = P[(T \geq 5) \cap (T \geq 4)] = P[T \geq 4] \cdot P[T \geq 5|T \geq 4] \\
&= P[T \geq 4] \cdot \{1 - P[4 \leq T < 5|T \geq 4]\} = P[T \geq 4] \cdot q_5 \\
&= P[T \geq 3] \cdot P[T \geq 4|T \geq 3] \cdot q_5 = P[T \geq 3] \cdot \{1 - P[3 \leq T < 4|T \geq 3]\} \cdot q_5 \\
&= P[T \geq 3] \cdot q_4 \cdot q_5 \\
&= = q_1 \cdot q_2 \cdot q_3 \cdot q_4 \cdot q_5
\end{aligned}$$

where $q_i = 1 - P[i-1 \leq T < i|T \geq i-1], i = 1, 2, ..., 5$. So if we can estimate q_i well, then we will get a very good estimate of $S(5)$. Note that $1 - q_i$ is the mortality rate $m(x)$ at year $x = i - 1$ by our definition.

Table 2.2: *Life-table estimate of $S(5)$ assuming censoring occurred at the end of interval*

duration $[t_{i-1}, t_i)$	$n(x)$	$d(x)$	$w(x)$	$\widehat{m}(x) = \frac{d(x)}{n(x)}$	$1 - \widehat{m}(x)$	$\widehat{S}^R(t_i) = \prod(1 - \widehat{m}(x))$
$[0, 1)$	146	27	3	0.185	0.815	0.815
$[1, 2)$	116	18	10	0.155	0.845	0.689
$[2, 3)$	88	21	10	0.239	0.761	0.524
$[3, 4)$	57	9	3	0.158	0.842	0.441
$[4, 5)$	45	1	3	0.022	0.972	0.432

Case 1: Let us first assume that anyone censored in an interval of time is censored at the end of that interval. Then we can estimate each $q_i = 1 - m(i-1)$ in the following way:

$$d(0) \sim \text{Bin}(n(0), m(0)) \Longrightarrow \widehat{m}(0) = \frac{d(0)}{n(0)} = \frac{27}{146} = 0.185, \quad \widehat{q}_1 = 1 - \widehat{m}(0) = 0.815$$

$$d(1)|H \sim \text{Bin}(n(1), m(1)) \Longrightarrow \widehat{m}(1) = \frac{d(1)}{n(1)} = \frac{18}{116} = 0.155, \quad \widehat{q}_2 = 1 - \widehat{m}(1) = 0.845$$

$$\cdots$$

where H means data history (i.e, data before the second interval).

The life table estimate would be computed as shown in Table 2.2. So the 5 year survival probability estimate $\widehat{S}^R(5) = 0.432$. (If the assumption that anyone censored in an interval of time is censored at the end of that interval is true, then the estimator $\widehat{S}^R(5)$ is approximately unbiased to $S(5)$.)

Of course, this estimate $\widehat{S}^R(5)$ will have variation since it was calculated from a sample. We need to estimate its variation in order to make inference on $S(5)$ (for example, construct a 95% CI for $S(5)$).

However, $\widehat{S}^R(5)$ is a product of 5 estimates ($\widehat{q}_1$ – $\widehat{q}_5$), whose variance is not easy to find. But we have

$$log(\widehat{S}^R(5)) = log(\widehat{q}_1) + log(\widehat{q}_2) + log(\widehat{q}_3) + log(\widehat{q}_4) + log(\widehat{q}_5).$$

So if we can find out the variance of each $log(\widehat{q}_i)$, we might be able to find out the variance of $log(\widehat{S}^R(5))$ and hence the variance of $\widehat{S}^R(5)$.

For this purpose, let us first introduce a very popular method in statistics: **delta method**:

Delta Method:

$$\begin{aligned} \text{If} \quad & \widehat{\theta} \overset{a}{\sim} \mathrm{N}(\theta, \sigma^2) \\ \text{then} \quad & f(\widehat{\theta}) \overset{a}{\sim} \mathrm{N}(f(\theta), [f'(\theta)]^2\sigma^2) \end{aligned}$$

Proof of delta method: If σ^2 is small, $\widehat{\theta}$ will be close to θ with high probability. We hence can expand $f(\widehat{\theta})$ about θ using Taylor expansion:

$$f(\widehat{\theta}) \approx f(\theta) + f'(\theta)(\widehat{\theta} - \theta).$$

We immediately get the (asymptotic) distribution of $f(\widehat{\theta})$ from this expansion.

Returning to our problem. Let $\widehat{\phi}_i = log(\widehat{q}_i)$. Using the delta method, the variance of $\widehat{\phi}_i$ is approximately equal to

$$\mathrm{var}(\widehat{\phi}_i) = \left(\frac{1}{q_i}\right)^2 \mathrm{var}(\widehat{q}_i).$$

Therefore we need to find out and estimate $\mathrm{var}(\widehat{q}_i)$. Of course, we also need to find out the covariances among $\widehat{\phi}_i$ and $\widehat{\phi}_j$ $(i \neq j)$. For this purpose, we need the following theorem:

Double expectation theorem (Law of iterated conditional expectation and variance): If X and Y are any two random variables (or vectors), then

$$\begin{aligned} &\mathrm{E}(X) = \mathrm{E}[\mathrm{E}(X|Y)] \\ &\mathrm{Var}(X) = \mathrm{Var}[\mathrm{E}(X|Y)] + \mathrm{E}[\mathrm{Var}(X|Y)] \end{aligned}$$

Since $\widehat{q}_i = 1 - \widehat{m}(i-1)$, we have

$$\mathrm{var}(\widehat{q}_i) \quad = \quad \mathrm{var}(\widehat{m}(i-1))$$

$$
\begin{aligned}
&= \mathrm{E}[\mathrm{var}(\widehat{m}(i-1)|H)] + \mathrm{var}[\mathrm{E}(\widehat{m}(i-1)|H)] \\
&= \mathrm{E}\left[\frac{m(i-1)[1-m(i-1)]}{n(i-1)}\right] + \mathrm{var}[m(i-1)] \\
&= m(i-1)[1-m(i-1)]\mathrm{E}\left[\frac{1}{n(i-1)}\right],
\end{aligned}
$$

which can be estimated by

$$\frac{\widehat{m}(i-1)[1-\widehat{m}(i-1)]}{n(i-1)}.$$

Hence the variance of $\widehat{\phi}_i = log(\widehat{q}_i)$ can be approximately estimated by

$$\left(\frac{1}{\widehat{q}_i}\right)^2 \frac{\widehat{m}(i-1)[1-\widehat{m}(i-1)]}{n(i-1)} = \frac{\widehat{m}(i-1)}{[1-\widehat{m}(i-1)]n(i-1)} = \frac{d}{(n-d)n}.$$

Now let us look at the covariances among $\widehat{\phi}_i$ and $\widehat{\phi}_j$ $(i \neq i)$. It is very amazing that they are all approximately equal to zero!

For example, let us consider the covariance between $\widehat{\phi}_1$ and $\widehat{\phi}_2$. Since $\widehat{\phi}_1 = log(\widehat{q}_1)$ and $\widehat{\phi}_2 = log(\widehat{q}_2)$, using the same argument for the delta method, we know that we only need to find out the covariance between $\widehat{q}_1$ and $\widehat{q}_2$, or equivalently, the covariance between $\widehat{m}(0)$ and $\widehat{m}(1)$. This can be seen from the following:

$$
\begin{aligned}
\mathrm{E}[\widehat{m}(0)\widehat{m}(1)] &= \mathrm{E}[\mathrm{E}[\widehat{m}(0)\widehat{m}(1)|n(0), d(0), w(0)]] \\
&= \mathrm{E}[\widehat{m}(0)\mathrm{E}[\widehat{m}(1)|n(0), d(0), w(0)]] \\
&= \mathrm{E}[\widehat{m}(0)m(1)] \\
&= m(1)\mathrm{E}[\widehat{m}(0)] \\
&= m(1)m(0) = \mathrm{E}[\widehat{m}(0)]\mathrm{E}[\widehat{m}(1)].
\end{aligned}
$$

Therefore, the covariance between $\widehat{m}(0)$ and $\widehat{m}(1)$ is zero. Similarly, we can show other covariances are zero. Hence,

$$\mathrm{var}(log(\widehat{S}^R(5))) = \mathrm{var}(\widehat{\phi}_1) + \mathrm{var}(\widehat{\phi}_2) + \mathrm{var}(\widehat{\phi}_3) + \mathrm{var}(\widehat{\phi}_4) + \mathrm{var}(\widehat{\phi}_5).$$

Let $\widehat{\theta} = log(\widehat{S}^R(5))$. Then $\widehat{S}^R(5) = e^{\widehat{\theta}}$. So

$$\mathrm{var}(\widehat{S}^R(5)) = (e^{\theta})^2\mathrm{var}(log(\widehat{S}^R(5))) = (S(5))^2[\mathrm{var}(\widehat{\phi}_1)+\mathrm{var}(\widehat{\phi}_2)+\mathrm{var}(\widehat{\phi}_3)+\mathrm{var}(\widehat{\phi}_4)+\mathrm{var}(\widehat{\phi}_5)],$$

which can be estimated by

$$\begin{aligned}\widehat{\text{var}}(\widehat{S}^R(5)) &= (\widehat{S}^R(5))^2\left[\frac{d(0)}{(n(0)-d(0))n(0)}+\frac{d(1)}{(n(1)-d(1))n(1)}+\frac{d(2)}{(n(2)-d(2))n(2)}\right.\\ &\qquad \left.+\frac{d(3)}{(n(3)-d(3))n(3)}+\frac{d(4)}{(n(4)-d(4))n(4)}\right]\\ &= (\widehat{S}^R(5))^2\sum_{i=0}^{4}\frac{d(i)}{[n(i)-d(i)]n(i)}. \qquad (2.1)\end{aligned}$$

Case 2: Let us assume that anyone censored in an interval of time is censored right at the beginning of that interval. Then the life table estimate would be computed as shown in Table 2.3. So the 5 year survival probability estimate = 0.400. (In this case, the estimator $\widehat{S}^L(5)$ is approximately unbiased to $S(5)$.)

The variance estimate of $\widehat{S}^L(5)$ is similar to that of $\widehat{S}^R(5)$ except that we need to change the "sample size" for each mortality estimate to $n - w$ in equation (2.1).

Table 2.3: *Life-table estimate of $S(5)$ assuming censoring occurred at the beginning of interval*

duration $[t_{i-1}, t_i)$	$n(x)$	$d(x)$	$w(x)$	$\widehat{m}(x) = \frac{d(x)}{n(x)-w(x)}$	$1 - \widehat{m}(x)$	$\widehat{S}^L(t_i) = \prod(1 - \widehat{m}(x))$
$[0, 1)$	146	27	3	0.189	0.811	0.811
$[1, 2)$	116	18	10	0.170	0.830	0.673
$[2, 3)$	88	21	10	0.269	0.731	0.492
$[3, 4)$	57	9	3	0.167	0.833	0.410
$[4, 5)$	45	1	3	0.024	0.976	0.400

The naive estimates range from 35% to 47.9% for the five year survival probability with the "complete case" (*i.e.*, eliminating anyone censored) estimator giving an estimate of 11.6%.

The life-table estimate ranged from 40% to 43.2% depending on whether we assume censoring occurred at the left (*i.e.*, beginning) or right (*i.e.*, end) of each interval.

More than likely censoring occurs during the interval. Thus $\widehat{S}^L$ and $\widehat{S}^R$ are not correct. A compromise is to use the following modification:

Table 2.4: *Life-table estimate of $S(5)$ assuming censoring occurred during the interval*

duration $[t_{i-1}, t_i)$	$n(x)$	$d(x)$	$w(x)$	$\widehat{m}(x) = \frac{d(x)}{n(x)-w(x)/2}$	$1-\widehat{m}(x)$	$\widehat{S}^{LT}(t_i) = \prod(1-\widehat{m}(x))$
$[0, 1)$	146	27	3	0.187	0.813	0.813
$[1, 2)$	116	18	10	0.162	0.838	0.681
$[2, 3)$	88	21	10	0.253	0.747	0.509
$[3, 4)$	57	9	3	0.162	0.838	0.426
$[4, 5)$	45	1	3	0.023	0.977	0.417

That is, when calculating the mortality estimate in each interval, we use $(n(x) - w(x)/2)$ as the "sample size". This number is often referred to as the *effective sample size.*

So the 5 year survival probability estimate $\widehat{S}^{LT}(5) = 0.417$, which is between $\widehat{S}^{L} = 0.400$ and $\widehat{S}^{R} = 0.432$.

Figure 2.2: *Life-table estimate of the survival probability for MI data*

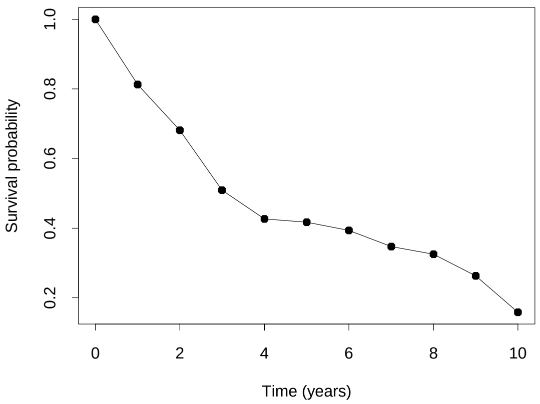


Figure 2.2 shows the life-table estimate of the survival probability assuming censoring occurred during interval. Here the estimates were connected using straight lines. No special significance should be given to this. From this figure, the median survival time is estimated to

be about 3 years.

The variance estimate of the life-tabble estimate $\widehat{S}^{LT}(5)$ is similar to equation (2.1) except that the sample size $n(i)$ is changed to $n(i) - w(i)/2$. That is

$$\widehat{\text{var}}(\widehat{S}^{LT}(5)) = (\widehat{S}^{LT}(5))^2 \sum_{i=0}^{4} \frac{d(i)}{[n(i) - w(i)/2 - d(i)][n(i) - w(i)/2]}. \tag{2.2}$$

Of course, we can also use the above formula to calculate the variance of $\widehat{S}^{LT}(t)$ at other time points. For example:

$$\begin{aligned}\widehat{\text{var}}(\widehat{S}^{LT}(1)) &= (\widehat{S}^{LT}(1))^2 \left\{\frac{d(0)}{[n(0) - w(0)/2 - d(0)][n(0) - w(0)/2]}\right\} \\ &= 0.813^2 \times \frac{27}{(146 - 3/2 - 27)(146 - 3/2)} = 0.813^2 \times 0.001590223 = 0.001051088.\end{aligned}$$

Therefore $SE(\widehat{S}^{LT}(1)) = \sqrt{0.001051088} = 0.0324$.

The calculation presented in Table 2.4 can be implemented using `Proc Lifetest` in `SAS`:

```
options ls=72 ps=60;

Data mi;
  input survtime number status;
  cards;
  0 27 1
  0  3 0
  1 18 1
  1 10 0
  2 21 1
  2 10 0
  3  9 1
  3  3 0
  4  1 1
  4  3 0
  5  2 1
  5 11 0
  6  3 1
  6  5 0
  7  1 1
  7  8 0
  8  2 1
  8  1 0
  9  2 1
  9  6 0
;

proc lifetest method=life intervals=(0 to 10 by 1);
  time survtime*status(0);
  freq number;
run;
```

Note that the number of observed events and withdrawals in $[t_{i-1}, t_i)$ were entered after t_{i-1} instead of t_i. Part of the output of the above `SAS` program is

```
                            The LIFETEST Procedure

                         Life Table Survival Estimates

                                                 Effective   Conditional
     Interval         Number       Number         Sample     Probability
  [Lower,   Upper)    Failed      Censored         Size       of Failure

      0         1       27            3           144.5          0.1869
      1         2       18           10           111.0          0.1622
      2         3       21           10            83.0          0.2530
      3         4        9            3            55.5          0.1622
      4         5        1            3            43.5          0.0230
      5         6        2           11            35.5          0.0563
      6         7        3            5            25.5          0.1176
      7         8        1            8            16.0          0.0625
      8         9        2            1            10.5          0.1905
      9        10        2            6             5.0          0.4000


                    Conditional
                    Probability                               Survival    Median
     Interval         Standard                                Standard   Residual
  [Lower,   Upper)     Error       Survival      Failure       Error     Lifetime

      0         1      0.0324       1.0000            0            0      3.1080
      1         2      0.0350       0.8131       0.1869       0.0324      4.4265
      2         3      0.0477       0.6813       0.3187       0.0393      5.2870
      3         4      0.0495       0.5089       0.4911       0.0438           .
      4         5      0.0227       0.4264       0.5736       0.0445           .
      5         6      0.0387       0.4166       0.5834       0.0446           .
      6         7      0.0638       0.3931       0.6069       0.0450           .
      7         8      0.0605       0.3469       0.6531       0.0470           .
      8         9      0.1212       0.3252       0.6748       0.0488           .
      9        10      0.2191       0.2632       0.7368       0.0558           .
```

Here the numbers in the column under `Conditional Probability of Failure` are the estimated mortality $\widehat{m}(x) = d(x)/(n(x) - w(x)/2)$.

The above lifetable estimation can also be implemented using R. Here is the R code:

```
> tis <- 0:10
> ninit <- 146
> nlost <- c(3,10,10,3,3,11,5,8,1,6)
> nevent <- c(27,18,21,9,1,2,3,1,2,2)
> lifetab(tis, ninit, nlost, nevent)
```

The output from the above *R* function is

```
      nsubs nlost nrisk nevent      surv         pdf     hazard    se.surv
0-1     146     3 144.5     27 1.0000000 0.186851211 0.20610687 0.00000000
1-2     116    10 111.0     18 0.8131488 0.131861966 0.17647059 0.03242642
2-3      88    10  83.0     21 0.6812868 0.172373775 0.28965517 0.03933747
3-4      57     3  55.5      9 0.5089130 0.082526440 0.17647059 0.04382194
4-5      45     3  43.5      1 0.4263866 0.009801991 0.02325581 0.04452036
5-6      41    11  35.5      2 0.4165846 0.023469556 0.05797101 0.04456288
6-7      28     5  25.5      3 0.3931151 0.046248831 0.12500000 0.04503654
7-8      20     8  16.0      1 0.3468662 0.021679139 0.06451613 0.04699173
8-9      11     1  10.5      2 0.3251871 0.061940398 0.21052632 0.04879991
9-10      8     6   5.0      2 0.2632467          NA         NA 0.05579906

           se.pdf  se.hazard
0-1   0.032426423 0.03945410
1-2   0.028930638 0.04143228
2-3   0.033999501 0.06254153
3-4   0.026163333 0.05859410
4-5   0.009742575 0.02325424
5-6   0.016315545 0.04097447
6-7   0.025635472 0.07202769
7-8   0.021195209 0.06448255
8-9   0.040488466 0.14803755
9-10           NA         NA
```

Note: Here the numbers in the column of `hazard` are the estimated hazard rates at the midpoint of each interval by assuming the true survival function $S(t)$ is a straight line in each interval. You can find an explicit expression for this estimator using the relation

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

and the assumption that the true survival function $S(t)$ is a straight line in $[t_{i-1}, t_i)$:

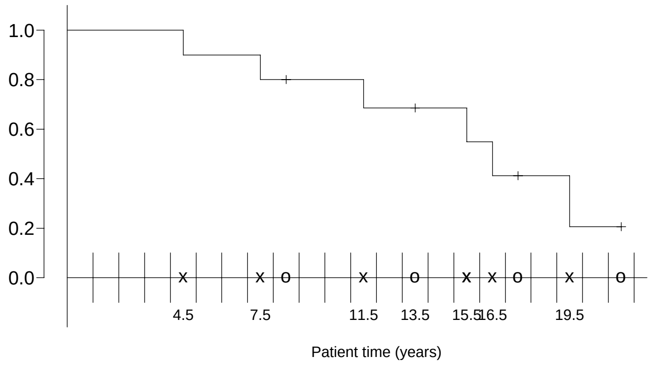
$$S(t) = S(t_{i-1}) + \frac{S(t_i) - S(t_{i-1})}{t_i - t_{i-1}}(t - t_{i-1}), \quad \text{for } t \in [t_{i-1}, t_i).$$

These estimates are very close to the mortality estimates we obtained before (the column under `Conditional Probability of Failure` in the `SAS` output.)

Kaplan-Meier Estimator

The **Kaplan-Meier** or **product limit** estimator is the limit of the life-table estimator when intervals are taken so small that only at most one distinct observation occurs within an interval. Kaplan and Meier demonstrated in a paper in JASA (1958) that this estimator is “maximum likelihood estimate”.

Figure 2.3: *An illustrative example of Kaplan-Meier estimator*



$$\begin{array}{lcccccccccccccccccccccc}
1-\widehat{m}(x): & 1 & 1 & 1 & 1 & \frac{9}{10} & 1 & 1 & \frac{8}{9} & 1 & 1 & 1 & \frac{6}{7} & 1 & 1 & 1 & \frac{4}{5} & \frac{3}{4} & 1 & 1 & \frac{1}{2} & 1 & 1 \\
\widehat{S}(t): & 1 & 1 & 1 & 1 & \frac{9}{10} & . & . & \frac{8}{10} & . & . & . & \frac{48}{70} & . & . & . & \frac{192}{350} & \frac{144}{350} & . & . & \frac{144}{700} & . & .
\end{array}$$

We will illustrate through a simple example shown in Figure 2.3 how the Kaplan-Meier estimator is constructed.

By convention, the Kaplan-Meier estimate is a **right continuous** step function which takes jumps only at the death time.

The calculation of the above KM estimate can be implemented using `Proc Lifetest` in `SAS` as follows:

```
Data example;
  input survtime censcode;
  cards;
  4.5 1
  7.5 1
  8.5 0
  11.5 1
  13.5 0
  15.5 1
  16.5 1
  17.5 0
  19.5 1
  21.5 0
;

Proc lifetest;
```

```
  time survtime*censcode(0);
run;
```

And part of the output from the above program is

```
                           The LIFETEST Procedure

                      Product-Limit Survival Estimates

                                           Survival
                                           Standard     Number       Number
 SURVTIME      Survival      Failure        Error       Failed        Left

   0.0000        1.0000            0            0          0           10
   4.5000        0.9000       0.1000       0.0949          1            9
   7.5000        0.8000       0.2000       0.1265          2            8
   8.5000*            .            .            .          2            7
  11.5000        0.6857       0.3143       0.1515          3            6
  13.5000*            .            .            .          3            5
  15.5000        0.5486       0.4514       0.1724          4            4
  16.5000        0.4114       0.5886       0.1756          5            3
  17.5000*            .            .            .          5            2
  19.5000        0.2057       0.7943       0.1699          6            1
  21.5000*            .            .            .          6            0
                           * Censored Observation
```

The above Kaplan-Meier estimate can also be obtained using *R* function `survfit()`. The code is given in the following:

```
> survtime <- c(4.5, 7.5, 8.5, 11.5, 13.5, 15.5, 16.5, 17.5, 19.5, 21.5)
> status <- c(1, 1, 0, 1, 0, 1, 1, 0, 1, 0)
> fit <- survfit(Surv(survtime, status), conf.type=c("plain"))
```

Then we can use *R* function `summary()` to see the output:

```
> summary(fit)
Call: survfit(formula = Surv(survtime, status), conf.type = c("plain"))

 time n.risk n.event survival std.err lower 95% CI upper 95% CI
  4.5     10       1    0.900  0.0949       0.7141        1.000
  7.5      9       1    0.800  0.1265       0.5521        1.000
 11.5      7       1    0.686  0.1515       0.3888        0.983
 15.5      5       1    0.549  0.1724       0.2106        0.887
 16.5      4       1    0.411  0.1756       0.0673        0.756
 19.5      2       1    0.206  0.1699       0.0000        0.539
```

Let $d(x)$ denote the number of deaths at time x. Generally $d(x)$ is either zero or one, but we allow the possibility of tied survival times in which case $d(x)$ may be greater than one. Let $n(x)$

denote the number of individuals at risk just prior to time x; *i.e.*, number of individuals in the sample who neither died nor were censored prior to time x. Then Kaplan-Meier estimate can be expressed as

$$KM(t) = \prod_{x \leq t} \left(1 - \frac{d(x)}{n(x)}\right).$$

Note: In the notation above, the product changes only at times x where $d(x) \geq 1$; , *i.e.*, only at times where we observed deaths.

Non-informative Censoring

In order that the life-table estimates give unbiased results there is an important assumption that individuals who are censored are at the same risk of subsequent failure as those who are still alive and uncensored. The risk set at any time point (the individuals still alive and uncensored) should be representative of the entire population alive at the same time. If this is the case, the censoring process is called **non-informative**. Statistically, if the censoring process is **independent** of the survival time, then we will automatically have non-informative censoring. Actually, we almost always mean independent censoring by non-informative censoring.

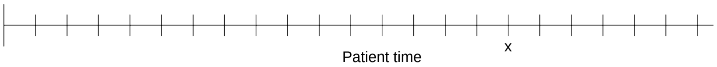
If censoring only occurs because of staggered entry, then the assumption of non-informative censoring seems plausible. However, when censoring results from loss to follow-up or death from a competing risk, then this assumption is more suspect. If at all possible censoring from these later situations should be kept to a minimum.

Greenwood's Formula for the Variance of the Life-table Estimator

The derivation given below is heuristic in nature but will try to capture some of the salient feature of the more rigorous treatments given in the theoretical literature on survival analysis. For this reason, we will use some of the notation that is associated with the "counting process" approach to survival analysis. In fact we have seen it when we discussed the life-table estimator.

It is useful when considering the product limit estimator to partition time into many small intervals, say, with interval length equal to Δx where Δx is small.

Figure 2.4: *Partition of time axis*



Let "x" denote some arbitrary time point on the grid above and define

- $Y(x)$ = number of individuals at risk (*i.e.*, alive and uncensored) at time point x.
- $dN(x)$ = number of observed deaths occurring in $[x, x + \Delta x)$.

Recall: Previously, $Y(x)$ was denoted by $n(x)$ and $dN(x)$ was denoted by $d(x)$.

It should be straightforward to see that "$w(x)$", the number of censored individuals in $[x, x+\Delta x)$, is equal to $\{[Y(x) - Y(x + \Delta x)] - dN(x)\}$.

Note: In theory, we should be able to choose Δx small enough so that $\{dN(x) > 0$ and $w(x) > 0\}$ should never occur. In practice, however, data may not be collected in that fashion, in which case, approximations such as those given with life-table estimators may be necessary.

With these definitions, the Kaplan-Meier estimator can be written as

$$KM(t) = \prod_{\text{all grid points } x \text{ such that } x+\Delta x \le t} \left\{1 - \frac{dN(x)}{Y(x)}\right\}, \quad \text{as } \Delta x \to 0,$$

which can be modified if "Δx" is not chosen small enough to be

$$LT(t) = \prod_{\text{all grid points } x \text{ such that } x+\Delta x \le t} \left\{1 - \frac{dN(x)}{Y(x) - w(x)/2}\right\},$$

where $LT(t)$ means life-table estimator.

If the sample size is large and Δx is small, then $\frac{dN(x)}{Y(x)}$ is a small number (*i.e.*, close to zero) and as long as x is not close to the right hand tail of the survival distribution (where $Y(x)$ may be very small). If this is the case, then

$$\exp\left\{-\frac{dN(x)}{Y(x)}\right\} \approx \left\{1-\frac{dN(x)}{Y(x)}\right\}.$$

Here we used the approximation $\mathrm{e}^x \approx 1+x$ when x is close to zero. This approximation is exact when $\frac{dN(x)}{Y(x)} = 0$.

Therefore, the Kaplan-Meier estimator can be approximated by

$$KM(t) \approx \prod_{\text{all grid points } x \text{ such that } x+\Delta x \leq t} \exp\left\{-\frac{dN(x)}{Y(x)}\right\} = \exp\left\{-\sum_{x<t}\frac{dN(x)}{Y(x)}\right\},$$

here and thereafter, $\{x<t\}$ means $\{\text{all grid points } x \text{ such that } x+\Delta x \leq t\}$.

If Δx is taken to be small enough so that all distinct times (either death times or withdrawal times) are represented at most once in any time interval, then the estimator $\sum_{x<t}\frac{dN(x)}{Y(x)}$ will be uniquely defined and will not be altered by choosing a *finer* partition for the grid of time points. In such a case the quantity $\sum_{x<t}\frac{dN(x)}{Y(x)}$ is sometimes represented as

$$\int_0^t \frac{dN(x)}{Y(x)}.$$

1. Basically, this estimator take the sum over all the distinct death times before time t of the number of deaths divided by the number at risk at each of those distinct death times.

2. The estimator $\sum_{x<t}\frac{dN(x)}{Y(x)}$ is referred to as the Nelson-Aalen estimator for the cumulative hazard function $\Lambda(t) = \int_0^t \lambda(x)dx$. That is

$$\widehat{\Lambda}(t) = \sum_{x<t}\frac{dN(x)}{Y(x)}.$$

   Recall that $S(t) = \exp(-\Lambda(t))$.

By the definition of an integral,

$$\Lambda(t) = \int_0^t \lambda(x)dx \approx \sum_{\text{grid points } x \text{ such that } x+\Delta x \leq t} \lambda(x)\Delta x.$$

By the definition of a hazard function,

$$\lambda(x)\Delta x \approx P[x \le T < x + \Delta x | T \ge x].$$

With independent censoring, it would seem reasonable to estimate $\lambda(x)\Delta x$, *i.e.*, "the conditional probability of dying in $[x, x + \Delta x)$ given being alive at time x" by $\frac{dN(x)}{Y(x)}$. Therefore we obtain the Nelson-Aalen estimator

$$\widehat{\Lambda}(t) = \sum_{x<t} \frac{dN(x)}{Y(x)}.$$

We will now show how to estimate the variance of the Nelson-Aalen estimator and then show how this will be used to estimate the variance of the Kaplan-Meier estimator.

For a grid point x, let $\mathcal{H}(x)$ denote the history of all deaths and censoring occurring up to time x.

$$\mathcal{H}(x) = \{dN(u), w(u); \text{for all values } u \text{ on our grid of points for } u < x\}.$$

Note the following

1. Conditional on $\mathcal{H}(x)$, we would know the value of $Y(x)$ (*i.e.*, the number of risk at time x) and that $dN(x)$ would follow a binomial distribution denoted as

$$dN(x)|\mathcal{H}(x) \sim \text{Bin}(Y(x), \pi(x)),$$

   where $\pi(x)$ is the Conditional probability of an individual dying in $[x, x + \Delta x)$ given that the individual was at risk at time x (*i.e.*, $\pi(x) = P[x \le T < x + \Delta x | T \ge x]$). Recall that this probability can be approximated by $\pi(x) \approx \lambda(x)\Delta x$.

2. The following are standard results for a binomially distributed random variable.

   (*a*) $\text{E}[dN(x)|\mathcal{H}(x)] = Y(x)\pi(x)$,

$$(b)\ \text{Var}[dN(x)|\mathcal{H}(x)] = Y(x)\pi(x)[1-\pi(x)],$$

$$(c)\ \text{E}\left[\left.\frac{dN(x)}{Y(x)}\right|\mathcal{H}(x)\right] = \pi(x),$$

$$(d)\ \text{E}\left\{\left.\left[\frac{Y(x)}{Y(x)-1}\right]\left[\frac{dN(x)}{Y(x)}\right]\left[\frac{Y(x)-dN(x)}{Y(x)}\right]\right|\mathcal{H}(x)\right\} = \pi(x)[1-\pi(x)].$$

Consider the Nelson-Aalen estimator $\widehat{\Lambda}(t) = \sum_{x<t}\frac{dN(x)}{Y(x)}$. We have

$$\begin{aligned}\text{E}[\widehat{\Lambda}(t)] &= \text{E}\left[\sum_{x<t}\frac{dN(x)}{Y(x)}\right] = \sum_{x<t}\text{E}\left[\frac{dN(x)}{Y(x)}\right]\\ &= \sum_{x<t}\text{E}\left[\text{E}\left[\left.\frac{dN(x)}{Y(x)}\right|\mathcal{H}(x)\right]\right] = \sum_{x<t}\pi(x)\\ &\approx \sum_{x<t}\lambda(x)\Delta x \approx \int_0^t \lambda(x)dx = \Lambda(t).\end{aligned}$$

Hence

- $\text{E}[\widehat{\Lambda}(t)] = \sum_{x<t}\pi(x)$.
- If we take Δx smaller and smaller, then in the limit $\sum_{x<t}\pi(x)$ goes to $\Lambda(t)$. Namely $\widehat{\Lambda}(t)$ is nearly unbiased to $\Lambda(t)$.

How to Estimate the Variance of $\widehat{\Lambda}(t)$

The definition of variance is given by

$$\begin{aligned}\text{Var}(\widehat{\Lambda}(t)) &= \text{E}[\widehat{\Lambda}(t) - \text{E}(\widehat{\Lambda}(t))]^2\\ &= \text{E}\left[\sum_{x<t}\frac{dN(x)}{Y(x)} - \sum_{x<t}\pi(x)\right]^2\\ &= \text{E}\left[\sum_{x<t}\left\{\frac{dN(x)}{Y(x)} - \pi(x)\right\}\right]^2.\end{aligned}$$

Note: The square of a sum of terms is equal to the sum of the squares plus the sum of all cross product terms. So the above expectation is equal to

$$\begin{aligned}&\text{E}\left[\sum_{x<t}\left\{\frac{dN(x)}{Y(x)}-\pi(x)\right\}^2 + \sum_{x\neq x'<t}\left\{\frac{dN(x)}{Y(x)}-\pi(x)\right\}\left\{\frac{dN(x')}{Y(x')}-\pi(x')\right\}\right]\\ =& \sum_{x<t}\text{E}\left[\frac{dN(x)}{Y(x)}-\pi(x)\right]^2 + \sum_{x\neq x'<t}\text{E}\left[\left\{\frac{dN(x)}{Y(x)}-\pi(x)\right\}\left\{\frac{dN(x')}{Y(x')}-\pi(x')\right\}\right]\end{aligned}$$

We will first demonstrate that the cross product terms have expectation equal to zero. Let us take one such term and let us say, without loss of generality, that $x < x'$.

$$\begin{aligned}
& \mathrm{E}\left[\left\{\frac{dN(x)}{Y(x)}-\pi(x)\right\}\left\{\frac{dN(x')}{Y(x')}-\pi(x')\right\}\right] \\
= \; & \mathrm{E}\left[\mathrm{E}\left[\left\{\frac{dN(x)}{Y(x)}-\pi(x)\right\}\left\{\frac{dN(x')}{Y(x')}-\pi(x')\right\}\middle|\mathcal{H}(x')\right]\right]
\end{aligned}$$

Note: Conditional on $\mathcal{H}(x')$, $dN(x), Y(x)$ and $\pi(x)$ are constant since $x < x'$. Therefore the above expectation is equal to

$$\mathrm{E}\left[\left\{\frac{dN(x)}{Y(x)}-\pi(x)\right\}\mathrm{E}\left[\left\{\frac{dN(x')}{Y(x')}-\pi(x')\right\}\middle|\mathcal{H}(x')\right]\right]$$

The inner conditional expectation is zero since

$$\mathrm{E}\left\{\frac{dN(x')}{Y(x')}\middle|\mathcal{H}(x')\right\}=\pi(x')$$

by $(2.c)$. Therefore we show that

$$\mathrm{E}\left[\left\{\frac{dN(x)}{Y(x)}-\pi(x)\right\}\left\{\frac{dN(x')}{Y(x')}-\pi(x')\right\}\right]=0.$$

Since the cross product terms have expectation equal to zero, this implies that

$$\mathrm{Var}(\widehat{\Lambda}(t))=\sum_{x<t}\mathrm{E}\left[\frac{dN(x)}{Y(x)}-\pi(x)\right]^2$$

Using the double expectation again, we get that

$$\begin{aligned}
& \mathrm{E}\left[\frac{dN(x)}{Y(x)}-\pi(x)\right]^2 \\
= \; & \mathrm{E}\left[\mathrm{E}\left[\left\{\frac{dN(x)}{Y(x)}-\pi(x)\right\}^2\middle|\mathcal{H}(x)\right]\right] \\
= \; & \mathrm{E}\left[\mathrm{Var}\left[\frac{dN(x)}{Y(x)}\middle|\mathcal{H}(x)\right]\right] \\
= \; & \mathrm{E}\left[\frac{\pi(x)[1-\pi(x)]}{Y(x)}\right].
\end{aligned}$$

Therefore, we have that

$$\mathrm{Var}(\widehat{\Lambda}(t))=\sum_{x<t}\mathrm{E}\left[\frac{\pi(x)[1-\pi(x)]}{Y(x)}\right].$$

If we wanted to estimate $\frac{\pi(x)[1-\pi(x)]}{Y(x)}$, then using $(2.d)$ we might think that

$$\frac{\frac{dN(x)}{Y(x)}\left[\frac{Y(x)-dN(x)}{Y(x)}\right]}{Y(x)-1}$$

may be reasonable. In fact, we would then use as an estimate for $\text{Var}(\widehat{\Lambda}(t))$ the following estimator; summing the above estimator over all grid points x such that $x+\Delta x \le t$.

$$\widehat{\text{Var}}(\widehat{\Lambda}(t)) = \sum_{x<t}\left[\frac{\frac{dN(x)}{Y(x)}\left[\frac{Y(x)-dN(x)}{Y(x)}\right]}{Y(x)-1}\right].$$

In fact, the above variance estimator is unbiased for $\text{Var}(\widehat{\Lambda}(t))$, which can be seen using the following argument:

$$\begin{aligned}
& \text{E}\left[\sum_{x<t}\frac{\frac{dN(x)}{Y(x)}\left[\frac{Y(x)-dN(x)}{Y(x)}\right]}{Y(x)-1}\right] \\
= & \sum_{x<t}\text{E}\left[\frac{\frac{dN(x)}{Y(x)}\left[\frac{Y(x)-dN(x)}{Y(x)}\right]}{Y(x)-1}\right] \\
= & \sum_{x<t}\text{E}\left[\text{E}\left[\left.\frac{\frac{dN(x)}{Y(x)}\left\{\frac{Y(x)-dN(x)}{Y(x)}\right\}}{Y(x)-1}\right|\mathcal{H}(x)\right]\right] \qquad \text{(double expectation again)} \\
= & \sum_{x<t}\text{E}\left[\frac{\pi(x)[1-\pi(x)]}{Y(x)}\right] \qquad \text{(by } (2.d))\\
= & \text{Var}[\widehat{\Lambda}(t)].
\end{aligned}$$

What this last argument shows is that an <u>unbiased estimator</u> for $\text{Var}[\widehat{\Lambda}(t)]$ is given by

$$\sum_{x<t}\left[\frac{\frac{dN(x)}{Y(x)}\left[\frac{Y(x)-dN(x)}{Y(x)}\right]}{Y(x)-1}\right].$$

<u>Note</u>: If the survival data are continuous (*i.e.*, no ties) and Δx is taken small enough, then $dN(x)$ would take on the values 0 or 1 only. In this case

$$\frac{\frac{dN(x)}{Y(x)}\left[\frac{Y(x)-dN(x)}{Y(x)}\right]}{Y(x)-1} = \frac{dN(x)}{Y^2(x)},$$

and

$$\widehat{\text{Var}}(\widehat{\Lambda}(t)) = \sum_{x<t}\frac{dN(x)}{Y^2(x)},$$

which is also written as

$$\int_0^t \frac{dN(x)}{Y^2(x)}.$$

Remark:

- We proved that the Nelson-Aalen estimator $\sum_{x<t} \frac{dN(x)}{Y(x)}$ is an unbiased estimator for $\sum_{x<t} \pi(x)$. We argued before that in the limit as Δx goes to zero,

$$\sum_{x<t} \frac{dN(x)}{Y(x)} \text{ becomes } \int_0^t \frac{dN(x)}{Y(x)}.$$

- We also argued that $\pi(x) \approx \lambda(x)\Delta x$, hence as Δx goes to zero, then

$$\sum_{x<t} \pi(x) \text{ goes to } \int_0^t \lambda(x)dx.$$

These two arguments taken together imply that

$$\int_0^t \frac{dN(x)}{Y(x)}$$

is an unbiased estimator of the cumulative hazard function

$$\Lambda(t) = \int_0^t \lambda(x)dx,$$

namely,

$$\mathrm{E}\left[\int_0^t \frac{dN(x)}{Y(x)}\right] = \Lambda(t).$$

- Since $\widehat{\Lambda}(t) = \sum_{x<t} \frac{dN(x)}{Y(x)}$ is made up of a sum of random variables that are conditionally uncorrelated, they have a "martingale" structure for which there exists a body of theory that enables us to show that

$\widehat{\Lambda}(t)$ is asymptotically normal with mean $\Lambda(t)$ and variance $\text{Var}[\widehat{\Lambda}(t)]$, which can be estimated unbiasedly by

$$\widehat{\text{Var}}(\widehat{\Lambda}(t)) = \sum_{x<t} \left[\frac{\frac{dN(x)}{Y(x)} \left[\frac{Y(x)-dN(x)}{Y(x)} \right]}{Y(x)-1} \right];$$

and in the case of no ties, by

$$\widehat{\text{Var}}(\widehat{\Lambda}(t)) = \sum_{x<t} \frac{dN(x)}{Y^2(x)}.$$

Let us refer to the estimated standard error of $\widehat{\Lambda}(t)$ by

$$\text{se}[\widehat{\Lambda}(t)] = \left[\sum_{x<t} \left[\frac{\frac{dN(x)}{Y(x)} \left[\frac{Y(x)-dN(x)}{Y(x)} \right]}{Y(x)-1} \right] \right]^{1/2}.$$

The unbiasedness and asymptotic normality of $\widehat{\Lambda}(t)$ about $\Lambda(t)$ allow us to form confidence intervals for $\Lambda(t)$ (at time t). Specifically, the $(1-\alpha)$th confidence interval for $\Lambda(t)$ is given by

$$\widehat{\Lambda}(t) \pm z_{\alpha/2} * \text{se}(\widehat{\Lambda}(t)),$$

where $z_{\alpha/2}$ is the $(1-\alpha/2)$th quantile of a standard normal distribution. That is, the random interval

$$[\widehat{\Lambda}(t) - z_{\alpha/2} * \text{se}(\widehat{\Lambda}(t)), \widehat{\Lambda}(t) + z_{\alpha/2} * \text{se}(\widehat{\Lambda}(t))]$$

covers the true value $\Lambda(t)$ with probability $1-\alpha$.

This result could also be used to construct confidence intervals for the survival function $S(t)$. This is seen by realizing that

$$S(t) = \text{e}^{-\Lambda(t)},$$

in which case the confidence interval is given by

$$[\text{e}^{-\widehat{\Lambda}(t)-z_{\alpha/2}*\text{se}(-\widehat{\Lambda}(t))}, \text{e}^{-\widehat{\Lambda}(t)+z_{\alpha/2}*\text{se}(\widehat{\Lambda}(t))}],$$

meaning that this random interval will cover the true value $S(t)$ with probability $1-\alpha$.

An example: We will use the hypothetical data shown in Figure 2.3 to illustrate the calculation of $\widehat{\Lambda}(t)$, $\widehat{\text{Var}\Lambda}(t)$, and confidence intervals for $\Lambda(t)$ and $S(t)$. For illustration, let us take $t = 17$. Note that there are no ties in this example. So

$$\begin{aligned}
\widehat{\Lambda}(t) &= \sum_{x<t} \frac{dN(x)}{Y(x)} = \int_0^t \frac{dN(x)}{Y(x)} = \frac{1}{10} + \frac{1}{9} + \frac{1}{7} + \frac{1}{5} + \frac{1}{4} = 0.804, \\
\widehat{\text{Var}}[\widehat{\Lambda}(t)] &= \sum_{x<t} \frac{dN(x)}{Y^2(x)} = \int_0^t \frac{dN(x)}{Y^2(x)} = \frac{1}{10^2} + \frac{1}{9^2} + \frac{1}{7^2} + \frac{1}{5^2} + \frac{1}{4^2} = 0.145, \\
\widehat{\text{se}}[\widehat{\Lambda}(t)] &= \sqrt{0.145} = 0.381.
\end{aligned}$$

So the 95% confidence interval for $\Lambda(t)$ is

$$0.804 \pm 1.96 \cdot 0.381 = [0.0572, 1.551].$$

and the Nelson-Aalen estimate of $S(t)$ is

$$\widehat{S}(t) = \mathrm{e}^{-\widehat{\Lambda}(t)} = \mathrm{e}^{-0.804} = 0.448.$$

The 95% confidence interval for $S(t)$ is

$$[\mathrm{e}^{-1.551}, \mathrm{e}^{-0.0572}] = [0.212, 0.944].$$

Note The above Nelson-Aalen estimate $\widehat{S}(t) = 0.448$ is different from (but close to) the Kaplan-Meier estimate $KM(t) = 0.411$. It should also be noted that above confidence interval for the survival probability $S(t)$ is not symmetric about the estimator $\widehat{S}(t)$. Another way of getting approximate confidence intervals for $S(t) = \mathrm{e}^{-\Lambda(t)}$ is by using the **delta** method. This method guarantees symmetric confidence intervals.

Hence a $(1-\alpha)$th confidence interval for $f(\theta)$ is given by

$$f(\widehat{\theta}) \pm z_{\alpha/2}|f'(\widehat{\theta})|\widehat{\sigma}.$$

In our case, $\Lambda(t)$ takes on the role of θ, $\widehat{\Lambda}(t)$ takes on the role of $\widehat{\theta}$, $f(\theta) = \mathrm{e}^{-\theta}$ so that $S(t) = f\{\Lambda(t)\}$. Since

$$|f'(\theta) = | - \mathrm{e}^{-\theta}| = \mathrm{e}^{-\theta}, \text{ and } \widehat{S}(t) = \mathrm{e}^{-\widehat{\Lambda}(t)}.$$

Consequently, using the delta method we get

$$\widehat{S}(t) \overset{a}{\sim} \mathrm{N}(S(t), [S(t)]^2 \mathrm{Var}[\widehat{\Lambda}(t)]),$$

and a $(1-\alpha)$th confidence interval for $S(t)$ is given by

$$\widehat{S}(t) \pm z_{\alpha/2}\{\widehat{S}(t) * \mathrm{se}[\widehat{\Lambda}(t)]\}.$$

<u>Remark</u>: Note that $[S(t)]^2\mathrm{Var}[\widehat{\Lambda}(t)]$ is an estimate of $\mathrm{Var}[\widehat{S}(t)]$, where $\widehat{S}(t) = \exp[-\widehat{\Lambda}(t)]$. Previously, we showed that the Kaplan-Meier estimator

$$KM(t) = \prod_{x<t}\left[1 - \frac{dN(x)}{Y(x)}\right]$$

was well approximated by $\widehat{S}(t) = \exp[-\widehat{\Lambda}(t)]$.

Thus a reasonable estimator of $\mathrm{Var}(KM(t))$ would be to use the estimator of $\mathrm{Var}[\exp(-\widehat{\Lambda}(t))]$, or (by using the delta method)

$$[\widehat{S}(t)]^2 \widehat{\mathrm{Var}}[\widehat{\Lambda}(t))] = [\widehat{S}(t)]^2 \sum_{x<t} \frac{dN(x)}{Y^2(x)}.$$

This is very close (asymptotically the same) as the estimator for the variance of the Kaplan-Meier estimator given by Greenwood. Namely

$$\widehat{\mathrm{Var}}\{KM(t)\} = \{KM(t)\}^2 \left[\sum_{x<t} \frac{dN(x)}{[Y(x) - w(x)/2][Y(x) - dN(x) - w(x)/2]}\right].$$

Note: `SAS` uses the above formula to calculate the estimated variance for the life-table estimate of the survival function, by replacing $KM(t)$ on both sides by $LT(t)$.

Note: The summation in the above equation can be viewed as the variance estimate for the cumulative hazard estimator defined by $\widehat{\Lambda}_{KM}(t) = -\log[KM(t)]$. Namely,

$$\mathrm{Var}\{\widehat{\Lambda}_{KM}(t)\} = \sum_{x<t} \frac{dN(x)}{[Y(x) - w(x)/2][Y(x) - dN(x) - w(x)/2]}.$$

In the example shown in Figure 2.3, using the delta-method approximation for getting a confidence interval with the Nelson-Aalen estimator, we get that a 95% CI for $S(t)$ (where t=17) is

$$\mathrm{e}^{-\widehat{\Lambda}(t)} \pm 1.96 * \mathrm{e}^{-\widehat{\Lambda}(t)}\mathrm{se}[\widehat{\Lambda}(t)] = e^{-0.801} \pm 1.96 * e^{-0.801} * 0.381 = [0.114, 0.784].$$

The estimated $\mathrm{se}[\widehat{S}(t)] = 0.171$.

If we use the Kaplan-Meier estimator, together with Greenwood's formula for estimating the variance, to construct a 95% confidence interval for $S(t)$, we would get

$$\begin{aligned}
KM(t) &= \left[1-\frac{1}{10}\right]\left[1-\frac{1}{9}\right]\left[1-\frac{1}{7}\right]\left[1-\frac{1}{5}\right]\left[1-\frac{1}{4}\right] = 0.411\\
\widehat{\mathrm{Var}}[KM(t)] &= 0.411^2\left\{\frac{1}{10*9}+\frac{1}{9*8}+\frac{1}{7*6}+\frac{1}{5*4}+\frac{1}{4*3}\right\} = 0.03077\\
\widehat{\mathrm{se}}[KM(t)] &= \sqrt{0.03077} = 0.175\\
\widehat{\mathrm{Var}}[\widehat{\Lambda}_{KM}(t)] &= \frac{1}{10*9}+\frac{1}{9*8}+\frac{1}{7*6}+\frac{1}{5*4}+\frac{1}{4*3} = 0.182\\
\mathrm{se}[\widehat{\Lambda}_{KM}(t)] &= 0.427.
\end{aligned}$$

Thus a 95% confidence interval for $S(t)$ is given by

$$KM(t) \pm 1.96 * \widehat{\mathrm{se}}[KM(t)] = 0.411 \pm 1.96 * 0.175 = [0.068, 0.754],$$

which is close to the confidence interval using delta method, considering the sample size is only 10. In fact the estimated standard errors for $\widehat{S}(t)$ and $KM(t)$ using delta method and Greenwood's formula are 0.171 and 0.175 respectively, which agree with each other very well.

Note: If we want to use R function `survfit()` to construct a confidence interval for $S(t)$ with the form $KM(t) \pm z_{\alpha/2} * \widehat{\mathrm{se}}[KM(t)]$, we have to specify the argument `conf.type=c("plain")` in `survfit()`. The default constructs the confidence interval for $S(t)$ by exponentiating the confidence interval for the cumulative hazard using the Kaplan-Meier estimator. For example, a 95% CI for $S(t)$ is $KM(t) * [e^{-1.96*\mathrm{se}[\widehat{\Lambda}_{KM}(t)]}, e^{1.96*\mathrm{se}[\widehat{\Lambda}_{KM}(t)]}] = 0.411 * [e^{-1.96*0.427}, [e^{1.96*0.427}] = [0.178, 0.949]$.

<u>Comparison of confidence intervals for $S(t)$</u>

1. exponentiating the 95% CI for cumulative hazard using Nelson-Aalen estimator: [0.212, 0.944].

2. Delta-method using Nelson-Aalen estimator: $[0.114, 0.784]$.

3. exponentiating the 95% CI for cumulative hazard using Kaplan-Meier estimator: $[0.178, 0.949]$.

4. Kaplan-Meier estimator together with Greenwood's formula for variance: $[0.068, 0.754]$.

These are relatively close and the approximations become better with larger sample sizes.

Of the different methods for constructing confidence intervals, "usually" the most accurate is based on exponentiating the confidence intervals for the cumulative hazard function based on Nelson-Aalen estimator. We don't feel that symmetry is necessarily an important feature that confidence interval need have.

Summary

1. We first estimate $S(t)$ by $KM(t) = \prod_{x<t}\left(1 - \frac{d(x)}{n(x)}\right)$, then estimate $\Lambda(t)$ by $\widehat{\Lambda}_{KM}(t) = -\log[KM(t)]$. Their variance estimates are

$$\begin{aligned}\widehat{\text{Var}}\{\widehat{\Lambda}_{KM}(t)\} &= \sum_{x<t}\frac{dN(x)}{[Y(x)-w(x)/2][Y(x)-dN(x)-w(x)/2]}\\ \widehat{\text{Var}}\{KM(t)\} &= \{KM(t)\}^2 * \widehat{\text{Var}}\{\widehat{\Lambda}_{KM}(t)\}.\end{aligned}$$

The confidence intervals for $S(t)$ can be constructed in two ways:

$$KM(t) \pm z_{\alpha/2} * \text{se}[KM(t)], \quad \text{or} \quad \mathrm{e}^{-\widehat{\Lambda}_{KM}(t) \pm z_{\alpha/2} * \text{se}[\widehat{\Lambda}_{KM}(t)]} = KM(t) * \mathrm{e}^{\pm z_{\alpha/2} * \text{se}[\widehat{\Lambda}_{KM}(t)]}$$

2. We first estimate $\Lambda(t)$ by Nelson-Aalen estimator $\widehat{\Lambda}(t) = \sum_{x<t}\frac{dN(x)}{Y(x)}$, then estimate $S(t)$ by $\widehat{S}(t) = \mathrm{e}^{-\widehat{\Lambda}(t)}$. Their variance estimates are given by

$$\begin{aligned}\widehat{\text{Var}}\{\widehat{\Lambda}(t)\} &= \sum_{x<t}\left[\frac{\frac{dN(x)}{Y(x)}\left[\frac{Y(x)-dN(x)}{Y(x)}\right]}{Y(x)-1}\right]\\ \widehat{\text{Var}}\{\widehat{S}(t)\} &= \{\widehat{S}(t)\}^2 * \widehat{\text{Var}}\{\widehat{\Lambda}(t)\}.\end{aligned}$$

The confidence intervals for $S(t)$ can also be constructed in two ways:

$$\widehat{S}(t) \pm z_{\alpha/2} * \text{se}[\widehat{S}(t)], \quad \text{or} \quad \mathrm{e}^{-\widehat{\Lambda}(t) \pm z_{\alpha/2} * \text{se}[\widehat{\Lambda}(t)]} = \widehat{S}(t) * \mathrm{e}^{\pm z_{\alpha/2} * \text{se}[\widehat{\Lambda}(t)]}.$$

Estimators of quantiles (such as median, first and third quartiles) of a distribution can be obtained by inverse relationships. This is most easily illustrated through an example.

Suppose we want to estimate the median $S^{-1}(0.5)$ or any other quantile $\varphi = S^{-1}(\theta)$; $0 < \theta < 1$. Then the point estimate of φ is obtained (using the Kaplan-Meier estimator of $S(t)$)

$$\widehat{\varphi} = KM^{-1}(\theta), \quad i.e., \quad KM(\widehat{\varphi}) = \theta.$$

An approximate $(1-\alpha)$th confidence interval for φ if given by $[\widehat{\varphi}_L, \widehat{\varphi}_U]$, where $\widehat{\varphi}_L$ satisfies

$$KM(\widehat{\varphi}_L) - z_{\alpha/2} * \text{se}[KM(\widehat{\varphi}_L)] = \theta$$

and $\widehat{\varphi}_U$ satisfies

$$KM(\widehat{\varphi}_U) + z_{\alpha/2} * \text{se}[KM(\widehat{\varphi}_U)] = \theta.$$

Proof: We prove this argument for a general estimator $\widehat{S}(t)$. So if we use the Kaplan-Meier estimator, then $\widehat{S}(t)$ is $KM(t)$. It can also be the Nelson-Aalen estimator. Then

$$\begin{aligned} P[\widehat{\varphi}_L < \varphi < \widehat{\varphi}_U] &= P[S(\widehat{\varphi}_U) < \theta < S(\widehat{\varphi}_L)] \text{ (note that } S(t) \text{ is decreasing and } S(\varphi) = \theta) \\ &= 1 - (P[S(\widehat{\varphi}_U) > \theta] + P[S(\widehat{\varphi}_L) < \theta]). \end{aligned}$$

Denote φ_U the solution to the equation

$$S(\varphi_U) + z_{\alpha/2} * \text{se}[\widehat{S}(\varphi_U)] = \theta.$$

Then $\widehat{\varphi}_U$ will be close to φ_U. Therefore,

$$\begin{aligned} P[S(\widehat{\varphi}_U) > \theta] &= P[S(\widehat{\varphi}_U) > \widehat{S}(\widehat{\varphi}_U) + z_{\alpha/2} * \text{se}[\widehat{S}(\widehat{\varphi}_U)]] \\ &= P\left[\frac{\widehat{S}(\widehat{\varphi}_U) - S(\widehat{\varphi}_U)}{\text{se}[\widehat{S}(\widehat{\varphi}_U)]} < -z_{\alpha/2}\right] \\ &\approx P\left[\frac{\widehat{S}(\varphi_U) - S(\varphi_U)}{\text{se}[\widehat{S}(\varphi_U)]} < -z_{\alpha/2}\right] \\ &\approx P[Z < -z_{\alpha/2}] \quad (Z \sim \text{N}(0,1)) \\ &= \frac{\alpha}{2}. \end{aligned}$$

Similarly, we can show that

$$P[S(\widehat{\varphi}_L) < \theta] \approx \frac{\alpha}{2}.$$

Therefore,

$$P[\widehat{\varphi}_L < \varphi < \widehat{\varphi}_U] \approx 1 - \left(\frac{\alpha}{2} + \frac{\alpha}{2}\right) = 1 - \alpha.$$

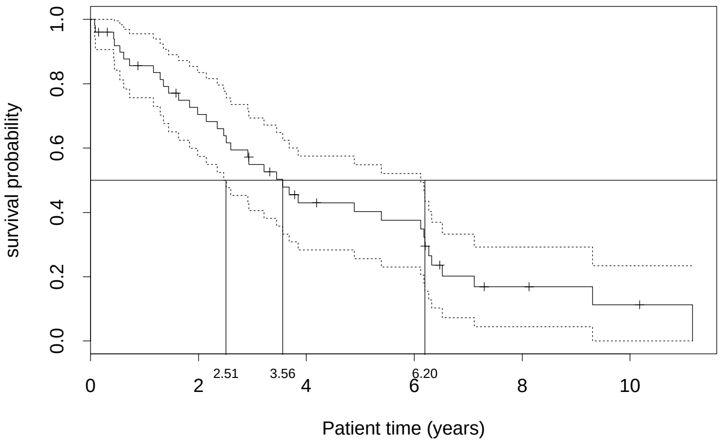
We illustrate this practice using a simulated data set generated using the following *R* commands

```
> survtime <- rexp(50, 0.2)
> censtime <- rexp(50, 0.1)
> status <- (survtime <= censtime)
> obstime <- survtime*status + censtime*(1-status)
> fit <- survfit(Surv(obstime, status))
> summary(fit)
Call: survfit(formula = Surv(obstime, status))

    time n.risk n.event survival std.err lower 95% CI upper 95% CI
  0.0747     50       1    0.980  0.0198       0.9420        1.000
  0.0908     49       1    0.960  0.0277       0.9072        1.000
  0.4332     46       1    0.939  0.0341       0.8747        1.000
  0.4420     45       1    0.918  0.0392       0.8446        0.998
  0.5454     44       1    0.897  0.0435       0.8161        0.987
  0.6126     43       1    0.877  0.0472       0.7887        0.974
  0.7238     42       1    0.856  0.0505       0.7622        0.961
  1.1662     40       1    0.834  0.0536       0.7356        0.946
  1.2901     39       1    0.813  0.0563       0.7097        0.931
  1.3516     38       1    0.791  0.0588       0.6843        0.915
  1.4490     37       1    0.770  0.0609       0.6594        0.899
  1.6287     35       1    0.748  0.0630       0.6342        0.882
  1.8344     34       1    0.726  0.0649       0.6094        0.865
  1.9828     33       1    0.704  0.0666       0.5850        0.847
  2.1467     32       1    0.682  0.0680       0.5610        0.829
  2.3481     31       1    0.660  0.0693       0.5373        0.811
  2.4668     30       1    0.638  0.0704       0.5140        0.792
  2.5135     29       1    0.616  0.0713       0.4910        0.773
  2.5999     28       1    0.594  0.0721       0.4683        0.754
  2.9147     27       1    0.572  0.0727       0.4459        0.734
  2.9351     25       1    0.549  0.0733       0.4228        0.713
  3.2168     24       1    0.526  0.0737       0.3999        0.693
  3.4501     22       1    0.502  0.0742       0.3762        0.671
  3.5620     21       1    0.478  0.0744       0.3528        0.649
  3.6795     20       1    0.455  0.0744       0.3298        0.627
  3.8475     18       1    0.429  0.0744       0.3056        0.603
  4.8888     16       1    0.402  0.0745       0.2800        0.578
  5.3910     15       1    0.376  0.0742       0.2551        0.553
  6.1186     14       1    0.349  0.0736       0.2307        0.527
  6.1812     13       1    0.322  0.0726       0.2069        0.501
  6.1957     12       1    0.295  0.0714       0.1837        0.474
  6.2686     10       1    0.266  0.0701       0.1584        0.445
  6.3252      9       1    0.236  0.0682       0.1340        0.416
  6.5206     7      1    0.202  0.0663        0.1065         0.385
  7.1127     6      1    0.169  0.0632        0.0809         0.352
  9.3017     3      1    0.112  0.0623        0.0379         0.333
 11.1589     1      1    0.000      NA            NA            NA
```

The true survival time has an exponential distribution with $\lambda = 0.2$/year (so the true mean is 5 years and median is $5 * log(2) \approx 3.5$ years). The (potential) censoring time is independent from the survival time and has an exponential distribution with $\lambda = 0.1$/year (so it is stochastically larger than the survival time). The Kaplan estimate (solid line) and its 95% confidence intervals (dotted lines) are shown in Figure 2.5, which is generated using R function `plot(fit, xlab="Patient time (years)", ylab="survival probability")`. Note that these CIs are constructed by exponentiating the CIs for $\Lambda(t)$. From this figure, the median survival time is estimated to be 3.56 years, with its 95% confidence interval $[2.51, 6.20]$.

Figure 2.5: *Illustration for constructing 95% CI for median survival time*



If we use symmetric confidence intervals of $S(t)$ to construct the confidence interval for the median of the true survival time, then we need to specify `conf.type=c("plain")` in `survfit()` as follows

```
> fit <- survfit(Surv(obstime, status), conf.type=c("plain"))
```

We get the following output using `summary()`

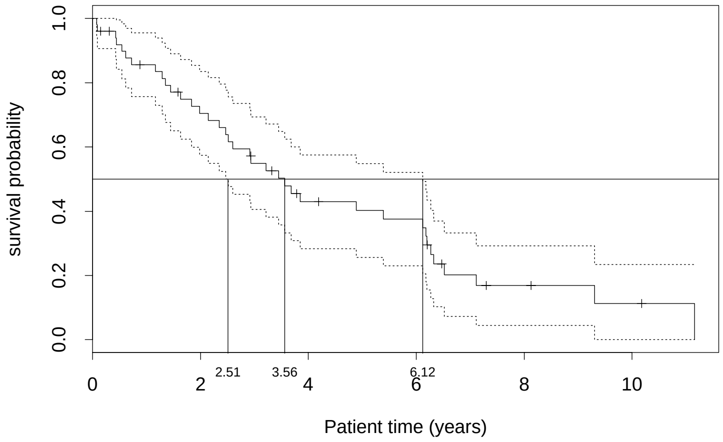
```
> summary(fit)
Call: survfit(formula = Surv(obstime, status), conf.type = c("plain"))

    time n.risk n.event survival std.err lower 95% CI upper 95% CI
  0.0747     50       1    0.980  0.0198       0.9412        1.000
  0.0908     49       1    0.960  0.0277       0.9057        1.000
  0.4332     46       1    0.939  0.0341       0.8723        1.000
  0.4420     45       1    0.918  0.0392       0.8414        0.995
  0.5454     44       1    0.897  0.0435       0.8121        0.983
  0.6126     43       1    0.877  0.0472       0.7839        0.969
  0.7238     42       1    0.856  0.0505       0.7567        0.955
  1.1662     40       1    0.834  0.0536       0.7292        0.939
  1.2901     39       1    0.813  0.0563       0.7025        0.923
  1.3516     38       1    0.791  0.0588       0.6763        0.907
  1.4490     37       1    0.770  0.0609       0.6506        0.890
  1.6287     35       1    0.748  0.0630       0.6245        0.872
  1.8344     34       1    0.726  0.0649       0.5988        0.853
  1.9828     33       1    0.704  0.0666       0.5736        0.835
  2.1467     32       1    0.682  0.0680       0.5487        0.815
  2.3481     31       1    0.660  0.0693       0.5242        0.796
  2.4668     30       1    0.638  0.0704       0.5001        0.776
  2.5135     29       1    0.616  0.0713       0.4763        0.756
  2.5999     28       1    0.594  0.0721       0.4528        0.735
  2.9147     27       1    0.572  0.0727       0.4296        0.715
  2.9351     25       1    0.549  0.0733       0.4055        0.693
  3.2168     24       1    0.526  0.0737       0.3818        0.671
  3.4501     22       1    0.502  0.0742       0.3570        0.648
  3.5620     21       1    0.478  0.0744       0.3326        0.624
  3.6795     20       1    0.455  0.0744       0.3087        0.600
  3.8475     18       1    0.429  0.0744       0.2834        0.575
  4.8888     16       1    0.402  0.0745       0.2565        0.548
  5.3910     15       1    0.376  0.0742       0.2302        0.521
  6.1186     14       1    0.349  0.0736       0.2046        0.493
  6.1812     13       1    0.322  0.0726       0.1796        0.464
  6.1957     12       1    0.295  0.0714       0.1552        0.435
  6.2686     10       1    0.266  0.0701       0.1283        0.403
  6.3252      9       1    0.236  0.0682       0.1024        0.370
  6.5206      7       1    0.202  0.0663       0.0724        0.332
  7.1127      6       1    0.169  0.0632       0.0447        0.293
  9.3017      3       1    0.112  0.0623       0.0000        0.235
 11.1589      1       1    0.000      NA           NA           NA
```

The Kaplan estimate (solid line) and its symmetric 95% confidence intervals (dotted lines) are shown in Figure 2.6. Note that the Kaplan estimate is the same as before. From this figure, the median survival time is estimated to be 3.56 years, with its 95% confidence interval $[2.51, 6.12]$.

Note: If we treat the censored data `obstime` as uncensored and fit an exponential model to it, then the "best" estimate of the median survival time is 2.5, with 95% confidence interval $[1.8, 3.2]$ (using the methodology to be presented in next chapter). These estimates severely underestimate the true median survival time 3.5 years.

Figure 2.6: *Illustration for constructing 95% CI for median survival time using symmetric CIs of $S(t)$*



Note:

If we want a CI for the quantile such as the median survival time with a different confidence level, say, 90%, then we need to construct 90% confidence intervals for $S(t)$. This can be done by specifying `conf.int=0.9` in the R function `survfit()`.

If we use `Proc Lifetest` in `SAS` to compute the Kaplan-Meier estimate, it will produce 95% confidence intervals for 25%, 50% (median) and 75% quantiles of the true survival time.

Other types of censoring and truncation:

- *Left censoring*: This kind of censoring occurs when the event of interest is only known to happen before a specific time point. For example, in a study of *time to first marijuana use* (example 1.17, page 17 of Klein & Moeschberger) 191 high school boys were asked "when did you first use marijuana?". Some answers were "I have used it but cannot recall when the first time was". For these boys, their *time to first marijuana use* is left censored at their current age. For the boys who never used marijuana, their *time to first marijuana use* is right censored at their current age. Of course, we got their exact *time to first marijuana* *use* for those boys who remembered when they first used it.

- *Interval censoring* occurs when the event of interest is only known to take place in an interval. For example, in a study to compare time to cosmetic deterioration of breasts for breast cancer patients treated with radiotherapy and radiotherapy + chemotherapy, patients were examined at each clinical visit for breast retraction and the breast retraction is only known to take place between two clinical visits or right censored at the end of the study. See example 1.18 on page 18 of Klein & Moeschberger.

- *Left truncation* occurs when the *time to event* of interest in the study sample is greater than a (left) truncation variable. For example, in a study of life expectancy (survival time measured from *birth* to *death*) using elderly residents in a retirement community (example 1.16, page 15 of Klein & Moeschberger), the individuals must survive to a sufficient age to enter the retirement community. Therefore, their survival time is left truncated by their age entering the community. Ignoring the truncation will lead to a biased sample and the survival time from the sample will over estimate the underlying life expectancy.

- *Right truncation* occurs when the *time to event* of interest in the study sample is less than a (right) truncation variable. A special case is when the study sample consists of only those individuals who have already experienced the event. For example, to study the induction period (also called latency period or incubation period) between infection with AIDS virus and the onset of clinical AIDS, the ideal approach will be to collect a sample of patients infected with AIDS virus and then follow them for some period of time until some of them develop clinical AIDS. However, this approach may be too lengthy and costly. An alternative approach is to study those patients who were infected with AIDS from a contaminated blood transfusion and later developed clinical AIDS. In this case, the total number of patients infected with AIDS is unknown. A similar approach can be used to study the induction time for pediatric AIDS. Children were infected with AIDS in utero or at birth and later developed clinical AIDS. But the study sample consists of children only known to develop AIDS. This sampling scheme is similar to the case-control design. See example 1.19 on page 19 of Klein & Moeschberger for more description and the data.

Note: The K-M survival estimation approach cannot be directly applied to the data with the above censorings and truncations. Modified K-M approach or others have to be used. Similar to right censoring case, the censoring time and truncation time are often assumed to be independent of the time to event of interest (survival time). Since right censoring is the most common censoring scheme, we will focus on this special case most of the time in this course. Nonparametric estimation of the survival function (or the cumulative distribution function) for the data with other censoring or truncation schemes can be found in Chapters 4 and 5 of Klein & Moeschberger.