Survival Analysis

Lecture 5

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Outline

Left truncation
- Left truncation
- Example
- Product limit estimator
- Using the survival package in R

Left and right censoring
- Left censoring
- Turnbull algorithm
- Example: marijuana data (Section 1.17)

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Left and right censoring

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Left truncation

- Left truncation happens when patients do not enter the study from the very beginning of the disease (late entry)
- The first time doctor sees them, the disease is already several weeks old
- The idea is that if they die within one week (say) then they will never enter the study
- The observation we have is conditional on the fact that they at least survive beyond the first week (or whatever the entering time)
- Terminology: left truncation or delayed entry
- When the truncation/entering time is 0, then there is no truncation

- Left truncation can happen together with right censoring
- Example:

$$(y_i, x_i) = (6, 17), (3, 13), (2, 9^+), (0, 16)$$

- This means the first subject enters the study at 6 month after infection and die at 17 month after infection
- The third subject enters the study at 2 month and is right censored at 9 month
- Notice the observations must have $x_i > y_i$

Left truncation

- For each individual j known:
- L_j: random age at which he/she enters the study
- T_j: censored or death time
- $t_1 < t_2 \ldots < t_D$: distinct death times
- d_i: number of individuals who experience the event of interest at time t_i
- Y_i: number at risk

- Y_i for right-censored data: number of individuals on study at time 0 with a study time of at least t_i
- For left-truncated data, Y_i is the number of individuals who entered the study prior to time t_i and who have a study time of at least t_i; i.e.
  - Y_i:number of individuals with $L_j \leq t_i \leq T_j$
- Use Y_i *redefined* for left-truncated data

- Product-Limit estimator of the survival function at a time t for the left truncated data is now an estimator of the probability of survival beyond t, conditional on survival to the smallest of the entry times L

$$P(X > t | X \geq L) = \frac{S(t)}{S(L)}$$

- Note that the number at risk could be quite small for small values of t_i (why?)
- If for some t_i we have $Y_i = d_i$ then, the Product-Limit estimator will be zero for all t beyond this point
- This happens although there are survivors and deaths beyond this point

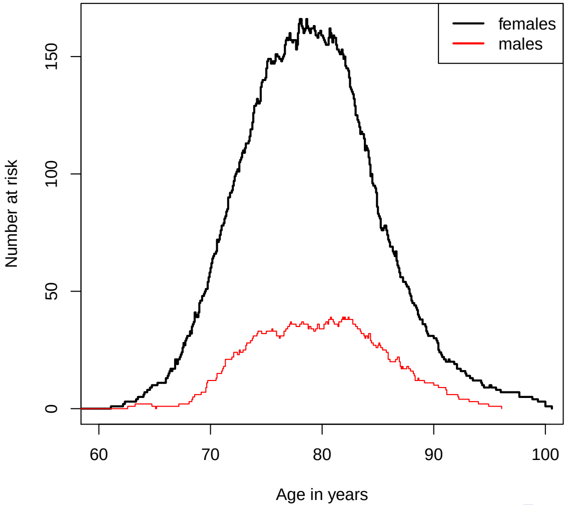
Example: data channing library(KMsurv)

```
> library(KMsurv)
> attach(channing); ?channing
> head(channing)
  obs death ageentry  age time gender
1   1     1     1042 1172  130      2
2   2     1      921 1040  119      2
3   3     1      885 1003  118      2
4   4     1      901 1018  117      2
5   5     1      808  932  124      2
6   6     1      915 1004   89      2
```

- *death*: Death status (1=dead, 0=alive)
- *ageentry*: Age of entry into retirement home, months
- *age*: Age of death or left retirement home, months
- *time*: Difference between the above two ages, months
- *gender*: Gender (1=male, 2=female)

- What is the truncation time? *Ages in months at which individuals enters the community*
- Look at the number of individuals at risk as a function of the age at which individuals die (for males and females)
- What do you expect?

Example


females
males
Number at risk
0
50
100
150
60
70
80
90
100
Age in years

- Consider data only for males

```
> library(KMsurv)
> attach(channing)
> index <- which(gender==1) #male
> tmp <- channing[index,]
```

- Sort by age entry to see when people start entering the risk set

```
sort(tmp[,3])
 [1]  751  759  782  806  817  820  821  823  830  835  835  836
[13]  836  837  843  846  847  847  852  853  854  856  856  856
[25]  863  865  865  866  871  871  875  876  878  878  879  883
[37]  885  886  890  891  893  894  898  900  906  906  909  915
[49]  919  919  921  923  925  926  936  936  938  943  943  946
[61]  953  953  955  955  956  959  960  962  962  964  966  967
[73]  967  969  969  971  978  978  981  982  984  984  988 1007
[85] 1010 1010 1016 1020 1021 1027 1036 1039 1041 1046 1051 1063
[97] 1073
```

Example

```
> head(sort(tmp[,3]))
[1] 751 759 782 806 817 820
> head(round(sort(tmp[,3]/12),0))
[1] 63 63 65 67 68 68
 > which(tmp[,3]==751)
[1] 86
```

- The risk set is empty until 751 months when the first individual enters the risk set
- A second individual enters the risk set at 759 months a third at 782 ...

- Find individuals who entered the risk set at time 751, 759, 782 months

```
> tmp[which(tmp[,3]==751),]
    obs death ageentry age time gender
451 451     1      751 777   26      1
> tmp[which(tmp[,3]==759),]
    obs death ageentry age time gender
455 455     1      759 781   22      1
> tmp[which(tmp[,3]==782),]
    obs death ageentry age time gender
366 366     1      782 909  127      1
```

- Recall

$$\prod_{i:t_i \le t}\left(1 - \frac{d_i}{Y_i}\right) \quad \textit{if } t_1 \le t$$

- Compute the product limit estimator based on this data
- The estimates are as follows

$$\widehat{S}(t) = \begin{cases} 1 & \text{if } t < 777 \\ 1/2 & \text{if } 777 \le t < 781 \\ 0 & \text{if } t \ge 781. \end{cases}$$

- The estimated survival function computed in this way has no meaning since the majority of the males in the study survive beyond 781 months

- Estimate the **conditional probability** of surviving beyond age t, given survival up to age a

$$S_a(t) = P(X > t | X \geq a)$$

- Do **not** estimate the unconditional survival function
- To estimate the conditional probability consider only those deaths that occur after age a

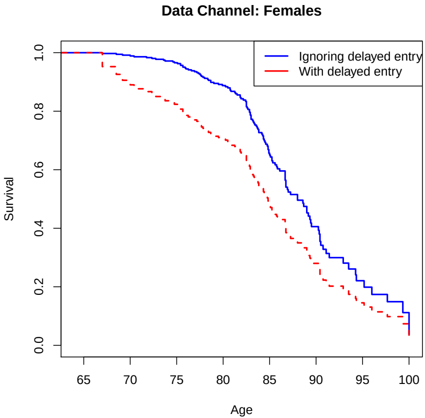
$$\widehat{S}_a(t) = \prod_{a \leq t_i \leq t} \left(1 - \frac{d_i}{Y_i}\right), \quad t \geq a$$

- Note that only deaths beyond time a are considered

What do you expect in terms of estimator for $S(t)$ for data Channing house if delayed entry is ignored?

What is important?

It is important to keep track on who is at risk!!!



- KM curve ignoring delayed entry overestimates the survival

```
> data(psych) #data from Section 1.15
> psych$time2 <- psych$age + psych$time
> head(psych)
  sex age time death time2
1   2  51    1     1    52
2   2  58    1     1    59
3   2  55    2     1    57
4   2  28   22     1    50
5   1  21   30     0    51
6   1  19   28     1    47
```

- Left truncation time is entered first as the variable `time`
- The event time (or censoring time) is `time2`
- The indicator variable δ_i for whether the event was observed is assigned to `event`

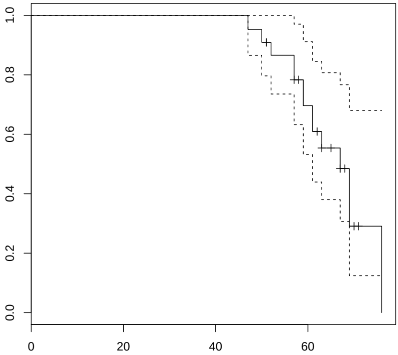
The data format is $(t_{entry}, t_{exit}, \delta)$

- R code:

```
> Surv(psych$age, psych$age+psych$time, psych$death)

 [1] (51,52 ] (58,59 ] (55,57 ] (28,50 ] (21,51+] (19,47 ] (25,57 ]
 [8] (48,59 ] (47,61 ] (25,61+] (31,62+] (24,57+] (25,58+] (30,67+]
[15] (33,68+] (36,61 ] (30,61+] (41,63 ] (43,69 ] (45,69 ] (35,70+]
[22] (29,63+] (35,65+] (32,67 ] (36,76 ] (32,71+]
```

```
> res <- survfit(Surv(age, time2, death) ~ 1, data=psych)
> res1 <- summary(res)
> res1

 time n.risk n.event entered censored survival std.err
   47     21       1       1        0    0.952  0.0465
   50     22       1       0        0    0.909  0.0613
   52     21       1       0        0    0.866  0.0721
   57     21       2       0        1    0.783  0.0856
   59     18       2       0        0    0.696  0.0957
   61     16       2       0        2    0.609  0.1016
   63     11       1       0        1    0.554  0.1064
   67      8       1       0        1    0.485  0.1134
   69      5       2       0        0    0.291  0.1261
   76      1       1       0        0    0.000     NaN
```

```
> plot(res)
```



- Kaplan Meier for *psych* data

Outline

Left censoring

- Left censored: data observed on the individual can be recorded as (T, δ) where $T = \max(X, C_l))$ and δ: indicator variable
$$\delta = \begin{cases} 1 & \text{if } T = X \\ 0 & \text{if } T = C_l \end{cases}$$
- Ex: childhood learning: Time-to-event: age at which a child learns to accomplish certain tasks in children learning centers
- Left censoring occurs if children can already perform the tasks hen they start their study at the centers
- Examples of pure left censoring are rare; more common are samples which include both left and right censoring

- Turnbull (1974) proposed an algorithm to estimate the product limit estimator which has no closed form and it is based on an iterative procedure
- Let $0 = t_0 < t_1 < \ldots < t_m$ be the grid of time points at which subjects are observed
- d_i: number of deaths at time t_i
- NB: t_i's are not event times, this implies that d_i may be zero for some points
- r_i: number of individuals right-censored at time t_i (subjects withdrawn from the study without experiencing the event at t_i)
- c_i: number of left-censored observations at time t_i (number for which the only information is that they experienced the event prior to t_i)

- Use information from left-censored observation (event has occurred at some $t_j \leq t_i$
- Estimates the probability that this event occurred at each possible $t_j < t_i$ based on an initial estimate of the survival function
- Compute an expected number of deaths at t_j (E-step) which is then used to update the estimate of the survival function
- Repeat the procedure until the estimated survival function stabilizes

- **Step 0:** $S_0(t_j)$: initial estimate of the survival function at t_j
  - Turnbull suggests the Product-limit estimate obtained by ignoring the left-censored data as initial value
- **Step (K+1) 1:** using the current estimate of S, estimate

$$p_{ij} = P(t_{j-1} < X \leq t_j | X \leq t_i)$$

as follows

$$\hat{p}_{ij} = \frac{S_k(t_{j-1}) - S_k(t_j)}{1 - S_k(t_i)}, \quad j \leq i$$

- **Step (K+1) 2:** use the results of the previous step to estimate the number of events at time t_j:
$\hat{d}_j = d_j + \sum_{i=j}^{m} c_i p_{ij}$

- **Step (K+1) 3:** Compute the Product-Limit estimator based on the estimated right-censored data with $\hat{d}_j$ events and r_j right-censored observations at t_i by ignoring the left-censored data
  - if $|S_{K+1}(t) - S_K(t)| \leq \epsilon$ for all t_i stop the procedure otherwise go to step 1
- Apply the algorithm to example Section 1.17

- In this study, 191 California high school boys were asked: When did you first use marijuana? The answers were
  - The exact ages (*uncensored observations*);
  - I never used it: *right-censored observations at the boys' current ages*;
  - I have used it but can not recall just when the first time was: *left-censored* observation

- Data table 1.8 page 17

```
> mar

   Age N.ExactOb N.YetToSmoke N.StartedToSmoke
1   10         4            0                0
2   11        12            0                0
3   12        19            2                0
4   13        24           15                1
5   14        20           24                2
6   15        13           18                3
7   16         3           14                2
8   17         1            6                3
9   18         0            0                1
10  19         4            0                0
```

- The initial Product-Limit estimator S_0 is obtained by ignoring the left-censored observations
- We need the following quantities for each time t_i:
  1. Number Left-Censored: c_i
  2. Number of events: d_i
  3. Number Right-Censored: r_i
  4. Number at risk: $Y_i = \sum_{j=1}^{m}(d_j + r_j)$
  5. compute the product limit estimator $S_0(t_i)$

- Reconstruct table 5.1 page 142

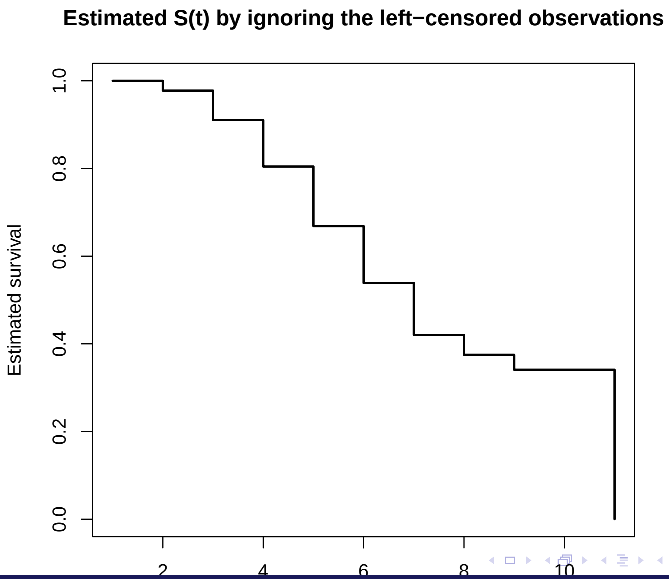
```
> # Age
> ti<-c(0,mar$Age)
> # Number left censored
> ci<-c(0,mar$N.StartedToSmoke)
> # Number of events
> di<-c(0,mar$N.ExactOb)
> # Number of right censored
> ri<-c(0,mar$N.YetToSmoke)
> n<-length(ti)
>
> ti
 [1]  0 10 11 12 13 14 15 16 17 18 19
> ci
 [1] 0 0 0 0 1 2 3 2 3 1 0
> di
 [1]  0  4 12 19 24 20 13  3  1  0  4
> ri
 [1]  0  0  0  2 15 24 18 14  6  0  0
>
```

Example: marijuana data (Section 1.17)

```
> Yi<-numeric(11)
> Si<-numeric(11)
> Yi[1]<-0
> # number at risk in time t1=1
> Yi[2]<-sum(di)+sum(ri)
> Yi
 [1]   0 179   0   0   0   0   0   0   0   0   0

> Si[1]<-1
> Si[2]<-1-di[2]/Yi[2]
> Si
 [1] 1.0000000 0.9776536 0.0000000 0.0000000 0.0000000
 [6] 0.0000000 0.0000000 0.0000000 0.0000000 0.0000000
[11] 0.0000000

> for(j in 2:(n-1))
+ {
+ # keep track of the number at risk; rj: number right censored
+ Yi[j+1]<-sum(di)-sum(di[1:j])+sum(ri)-sum(ri[1:j])
+ Si[j+1]<-Si[j]*(1-di[j+1]/Yi[j+1])
+ }
> table5.1<-cbind(ti,ci,di,ri,Yi,Si)
> table5.1<-data.frame(table5.1)
```

Example: marijuana data (Section 1.17)

```
> table5.1
   ti ci di ri  Yi         Si
1   0  0  0  0   0 1.0000000
2  10  0  4  0 179 0.9776536
3  11  0 12  0 175 0.9106145
4  12  0 19  2 163 0.8044693
5  13  1 24 15 142 0.6685026
6  14  2 20 24 103 0.5386963
7  15  3 13 18  59 0.4200005
8  16  2  3 14  28 0.3750005
9  17  3  1  6  11 0.3409095
10 18  1  0  0   4 0.3409095
11 19  0  4  0   4 0.0000000
> sum(table5.1$di)
[1] 100
> sum(table5.1$ri)
[1] 79

> # plot survival S(t)
 plot(table5.1$Si, type="s", xlab="Age", ylab="Estimated survival",
 + lwd=2, main="Estimated S(t) by ignoring the left-censored
 + observations")
```


Estimated S(t) by ignoring the left−censored observations
Estimated survival
0.0
0.2
0.4
0.6
0.8
1.0
2
4
6
8
10

- Use the table obtained to estimate $p_{ij} = P(t_{j-1} < X \leq t_j | X \leq t_i)$ as $\hat{p}_{ij} = \frac{S_k(t_{j-1}) - S_k(t_j)}{1 - S_k(t_i)}$
- We need to estimate only for i such that $c_i > 0$ (c_i: left-censored observation)
- For the left-censored observation at time t_4 we have (see table 5.1 first column next slide)

$$p_{41} = \frac{1 - 0.978}{1 - 0.669} = 0.067; \; p_{42} = \frac{0.978 - 0.911}{1 - 0.669} = 0.202$$

$$p_{43} = \frac{0.911 - 0.804}{1 - 0.669} = 0.320; \; p_{44} = \frac{0.804 - 0.669}{1 - 0.669} = 0.410$$

- Perform similar computations to estimate values of p_{ij}

Example: marijuana data (Section 1.17)

```
> table5.1
   ti ci di ri  Yi        Si
1   0  0  0  0   0 1.0000000
2  10  0  4  0 179 0.9776536
3  11  0 12  0 175 0.9106145
4  12  0 19  2 163 0.8044693
5  13  1 24 15 142 0.6685026
6  14  2 20 24 103 0.5386963
7  15  3 13 18  59 0.4200005
8  16  2  3 14  28 0.3750005
9  17  3  1  6  11 0.3409095
10 18  1  0  0   4 0.3409095
11 19  0  4  0   4 0.0000000
```

```
> # Find position left censored observations
> val <- which(ci>0)-1
> val
[1] 4 5 6 7 8 9
> table5.2<-matrix(rep(0,9*length(val)),nrow=9, ncol=length(val))
> table5.2<-data.frame(table5.2)
> colnames(table5.2)<-val
```

- estimate p_{ij} by $\hat{p}_{ij} = \frac{S_k(t_{j-1}) - S_k(t_j)}{1 - S_k(t_i)}$ for $j \leq i$

```
> for(j in val)
+ {
+ i<-which(val==j)
+ for(k in 1:j)
+ {
+ # estimate p_{ij}
+ table5.2[k,i]<-(Si[k]-Si[k+1])/(1-Si[j+1])
+ }
+ }
```

```
> table5.2
          4          5          6          7          8          9
1 0.0674104 0.04844177 0.03852826 0.03575422 0.03390486 0.03390486
2 0.2022312 0.14532532 0.11558477 0.10726265 0.10171457 0.10171457
3 0.3201994 0.23009842 0.18300921 0.16983252 0.16104807 0.16104807
4 0.4101590 0.29474430 0.23442544 0.21754678 0.20629434 0.20629434
5 0.0000000 0.28139019 0.22380422 0.20769029 0.19694767 0.19694767
6 0.0000000 0.00000000 0.20464810 0.18991341 0.18009028 0.18009028
7 0.0000000 0.00000000 0.00000000 0.07200014 0.06827599 0.06827599
8 0.0000000 0.00000000 0.00000000 0.00000000 0.05172423 0.05172423
9 0.0000000 0.00000000 0.00000000 0.00000000 0.00000000 0.00000000
```

- Column 1: values of p_{ij} for $i = 4$ and $j = 1, \ldots, 4$ ($j \leq i$) $(p_{41}, p_{42}, p_{43}, p_{44})$
- $\vdots$
- Column 9: values of p_{ij} for $i = 9$ and $j = 1, \ldots, 9$ ($j \leq i$) $(p_{91}, p_{92}, \ldots, p_{99})$

- Using the result from Step 1 estimate number of events at time t_j by: $\hat{d}_j = d_j + \sum_{i=j}^{m} c_i p_{ij}$

$$\hat{d}_1 = 4 + 0.067 \times 1 + 0.048 \times 2 + 0.039 \times 3 + 0.036 \times 2+$$

$$+0.034 \times 3 + 0.034 \times 1 = 4.487 = d_1 + \sum_{i=4}^{9} p_{i1} c_i$$

- Values p_{ij} are found in Table 5.2; values c_i are the number of left observations given in the data
- Use these values to compute the updated estimate of the survival function $S_1(t)$
- Repeat the procedure until difference is small

- Estimate $\hat{d}_j = d_j + \sum_{i=1}^{m} c_i p_{ij}$

```
> tj<-ti # age
> dj<-di # number of events
> rj<-ri # number right censored
> # find c_i
> cj<-ci[val+1]
>
> for(j in 2:(n-1))
+ { # estimate d_j
+ dj[j]<-dj[j]+sum(cj*table5.2[j-1,])
+ }
> dj
 [1]  0.000000  4.487007 13.461020 21.313281 26.963195
 [6] 22.437364 14.714132  3.417104  1.206897  0.000000
[11]  4.000000
```

```
> Yj<-numeric(11)
> Sj<-numeric(11)
>
> Yj[1]<-0
> Yj[2]<-sum(dj)+sum(rj)
> Sj[1]<-1
> Sj[2]<-1-dj[2]/Yj[2]
> for(j in 2:(n-1))
+ {
+ # keep track of the number at risk; dj: events at time tj
+ # obtained with formula given in Step 2 of the algorithm;
+ # rj: number right censored at time tj (column 5 table 5.1);
+ Yj[j+1]<-sum(dj)-sum(dj[1:j])+sum(rj)-sum(rj[1:j])
+ # estimate S(t) with product limit estimator
+ Sj[j+1]<-Sj[j]*(1-dj[j+1]/Yj[j+1])
+ }
>
```

- Crucial ingredients: the **risk set** Y_i and the **number of events** d_i at every time point t_i

- The estimated survival $\hat{S}(t)$ is computed with the usual product limit estimator $\prod_{t_i \leq t}(1 - d_i/Y_i)$ based on the estimated right-censored data with: $\hat{d}_i$ events; r_i: right-censored observations at time t_i
- The computations are done by **ignoring** the left-censored data
- The values $\hat{d}_j = d_j + \sum_{i=j}^{m} c_i p_{ij}$ are then used in the code to compute the updated estimate of the survival function $S_1(t)$
- If this estimate, $\hat{S}_1(t)$ is close to $\hat{S}_0(t)$ for all t_i , stop the procedure; if not, go to step 1.

Example: marijuana data (Section 1.17)

```
> table5.3<-cbind(tj,dj,rj,Yj,Sj)
> table5.3<-data.frame(table5.3)
> table5.3
   tj        dj rj        Yj        Sj
1   0  0.000000  0   0.00000 1.0000000
2  10  4.487007  0 191.00000 0.9765078
3  11 13.461020  0 186.51299 0.9060313
4  12 21.313281  2 173.05197 0.7944434
5  13 26.963195 15 149.73869 0.6513893
6  14 22.437364 24 107.77550 0.5157791
7  15 14.714132 18  61.33813 0.3920511
8  16  3.417104 14  28.62400 0.3452485
9  17  1.206897  6  11.20690 0.3080679
10 18  0.000000  0   4.00000 0.3080679
11 19  4.000000  0   4.00000 0.0000000
```

- Plot estimated survival $S_0(t)$ obtained in Table 5.1 together with estimated $S_1(t)$ from table 5.3

```
> plot(table5.1$Si, type="s", xlab="Age", ylab="Estimated survival",
+  lwd=2, col="red")
> lines(table5.3$Sj, type="s", col="blue", lwd=2)
> legend("bottomleft",c("Estimated initial S(t)","Estimated S(t)
+ first step"), lwd=2,col=c("blue","red"))#lty=1:2)
```

Example: marijuana data (Section 1.17)