TMA4275 LIFETIME ANALYSIS

Slides 7: Exponential distribution, TTT plot, logrank test

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Consider lifetime T with given cumulative hazard function $Z(t)$. After we observe T, we may compute $Z(T)$, which is hence a random variable since T is a random variable. The following result says that this random variable is exponentially distributed with parameter 1, whatever be the distribution of T. The important point is of course that it is T's own $Z(t)$ that is used to transform T.

Proof: Recall that $Z(t) = -\ln R(t)$ and $R(t) = P(T > t)$. Thus we have:

$$\begin{aligned} P(Z(T) > z) &= P(-\ln R(T) > z) = P(\ln R(T) < -z) \\ &= P(R(T) < e^{-z}) = P(T > R^{-1}(e^{-z})) \\ &= R(R^{-1}(e^{-z})) = e^{-z} \end{aligned}$$

so $Z(T) \sim \text{expon}(1)$. Here we used that $R(t)$ is decreasing and hence has a decreasing inverse function R^{-1}.

- Suppose $T \sim \text{expon}(\lambda)$. Then $z(t) = \lambda$ and $Z(t) = \lambda t$. Thus the result says that $Z(T) = \lambda T \sim \text{expon}(1)$. But this also follows from the previous Property 2 for the exponential distribution.
- Suppose then $T \sim \text{Weibull}(\alpha, \theta)$, so that $Z(t) = \left(\frac{t}{\theta}\right)^{\alpha}$. Then

$$Z(T) = \left(\frac{T}{\theta}\right)^{\alpha}$$

so

$$\begin{aligned} P(Z(T) > z) &= P(\left(\frac{T}{\theta}\right)^{\alpha} > z) = P\left(\frac{T}{\theta} > z^{1/\alpha}\right) \\ &= P(T > \theta z^{1/\alpha}) = R(\theta z^{1/\alpha}) \\ &= e^{-\left(\frac{\theta z^{1/\alpha}}{\theta}\right)^{\alpha}} = e^{-z} \end{aligned}$$

i.e. $W \sim \text{expon}(1)$.

Write the result as

$$\int_0^T z(u)du = V$$

where $V \sim \text{expon}(1)$.

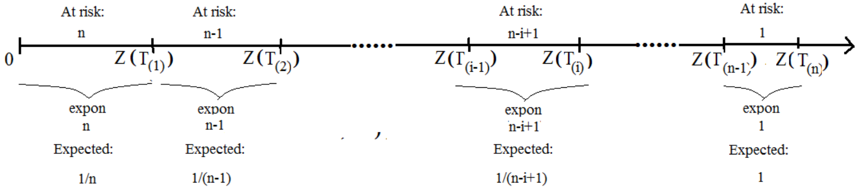
If we think of V as "given" to us at birth, drawn from an expon(1)-distribution, then our lifetime T is determined by the behavior of the hazard function $z(t)$. Thus the lifetime will be longer if we are able to reduce our hazard throughout life.

The result can also be used to simulate lifetimes $T_1, \ldots, T_n$ for a sample of units: Draw independent expon(1)-variables $V_1, \ldots, V_n$ and compute the corresponding T_i as

$$T_i = Z^{-1}(V_i), \quad i = 1, \ldots, n$$

Suppose data are n independent observations $T_1, \ldots, T_n$ of the lifetime T with cumulative hazard function $Z(t)$, with no censored observations.

Then $Z(T_1), \ldots, Z(T_n)$ are i.i.d. expon(1), and from figure:



$$E\left(Z(T_{(i)}\right) = \frac{1}{n} + \frac{1}{n-1} + \cdots \frac{1}{n-i+1} \quad \text{for } i = 1, 2, \ldots, n$$

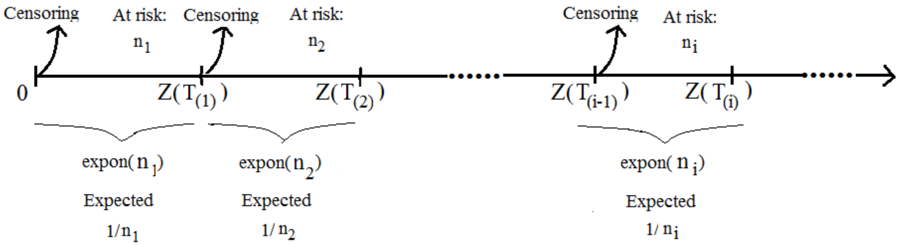
Nelson: For noncensored data, estimate the function $Z(t)$ by letting

$$\hat{Z}(T_{(i)}) = \frac{1}{n} + \frac{1}{n-1} + \cdots + \frac{1}{n-i+1} \quad \text{for } i = 1, 2, \ldots, n$$

(and let $\hat{Z}(t)$ be constant between observations).

Let $T_{(1)} < T_{(2)} < \cdots$ be the observed *failure* times.

Assume that the censored observations are always deleted from the data in the immediate beginning of each interval $(T_{(i-1)}, T_{(i)})$, and let n_i be the number at risk after deletion of the censored ones.



Nelson-Aalen: Estimate the function $Z(t)$ by letting

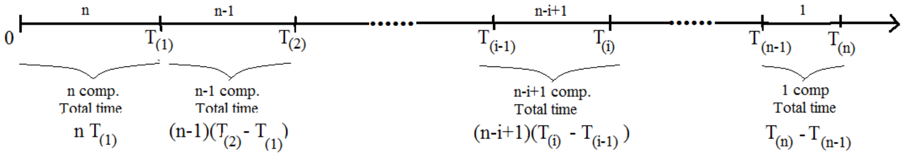
$$\hat{Z}(T_{(i)}) = \frac{1}{n_1} + \frac{1}{n_2} + \cdots + \frac{1}{n_i} \quad \text{for } i = 1, 2, \ldots$$

(and let $\hat{Z}(t)$ be constant between observations).

TOTAL TIME ON TEST, $\mathcal{T}(t)$

n components are put on test at time $t = 0$ and observed until failure.

Let $\mathcal{T}(t) =$ *Total Time on Test* at time t.



$$
\begin{aligned}
Y_1 &= \mathcal{T}(T_{(1)}) = nT_{(1)} \\
Y_2 &= \mathcal{T}(T_{(2)}) = \mathcal{T}(T_{(1)}) + (n-1)(T_{(2)} - T_{(1)}) = T_{(1)} + (n-1)T_{(2)} \\
&\vdots \\
Y_i &= \mathcal{T}(T_{(i)}) = \mathcal{T}(T_{(i-1)}) + (n-i+1)(T_{(i)} - T_{(i-1)}) \\
&= T_{(1)} + T_{(2)} + \cdots + T_{(i-1)} + (n-i+1)T_{(i)} \\
&\vdots \\
Y_n &= \mathcal{T}(T_{(n)}) = \mathcal{T}(T_{(n-1)}) + (T_{(n)} - T_{(n-1)}) = T_{(1)} + T_{(2)} + \cdots + T_{(n)}
\end{aligned}
$$

Recall:

- n components are put on test at time $t = 0$ and observed until failure.
- $\mathcal{T}(t) =$ *Total Time on Test* at time t.

A non-normalized TTT-plot would be a plot of the points

$$(i, \mathcal{T}(T_{(i)})), \; i = 1, \cdots, n.$$

The convention is, however, to plot the points

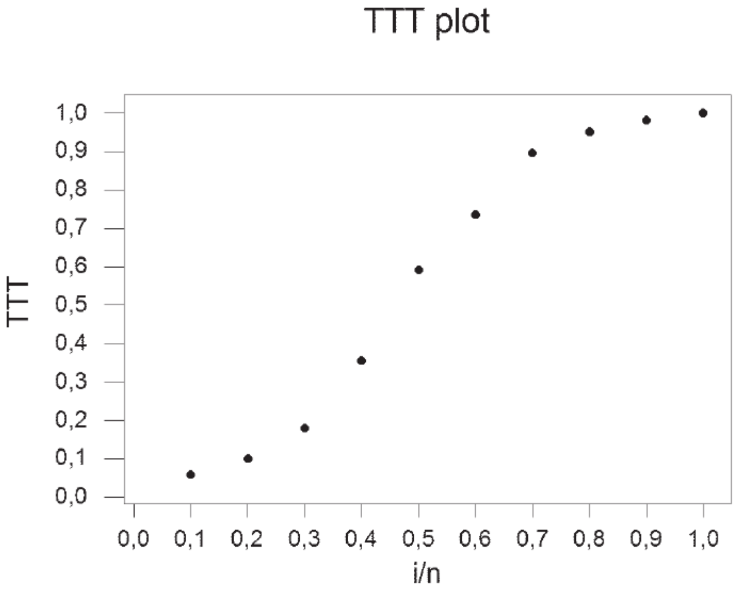
$$\left(\frac{i}{n}, \frac{\mathcal{T}(T_{(i)})}{\mathcal{T}(T_{(n)})}\right) \quad \text{or} \quad \left(\frac{i}{n}, \frac{Y_i}{Y_n}\right), \qquad \text{for } i = 1, 2, \ldots, n$$

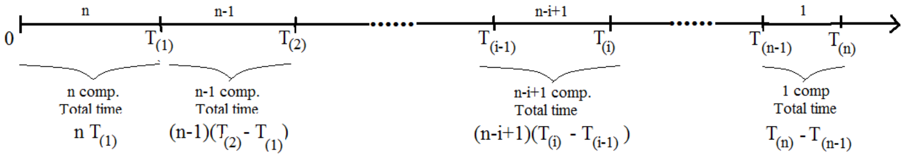
The last point is thus (1,1), so this plot is always in the unit square.

$n = 10$; uncensored observations $T_{(1)}, \ldots, T_{(10)}$.

Row	Time	TTT interval	TTT cum	i/n	TTT
1	6,3	10*6,3 = 63,0	63,0	0,1	0,05943
2	11,0	9*4,7 = 42,3	105,3	0,2	0,09934
3	21,5	8*10,5 = 84,0	189,3	0,3	0,17858
4	48,4	7*27,9 = 188,3	377,6	0,4	0,35623
5	90,1	6*41,7 = 250,2	627,8	0,5	0,59226
6	120,2	5*30,1 = 150,5	778,3	0,6	0,73425
7	163,0	4*42,8 = 171,2	949,5	0,7	0,89575
8	182,5	3*19,5 = 58,5	1008,0	0,8	0,95094
9	198,0	2*15,5 = 31,0	1039,0	0,9	0,98019
10	219,0	1*21,0 = 21,0	1060,0	1,0	1,00000

EXAMPLE: TTT-plot





Recall that **if** $T_1, \ldots, T_n$ are expon(λ), then

$$(n-i+1)(T_{(i)} - T_{(i-1)}) \sim \text{expon}(\lambda),$$

so

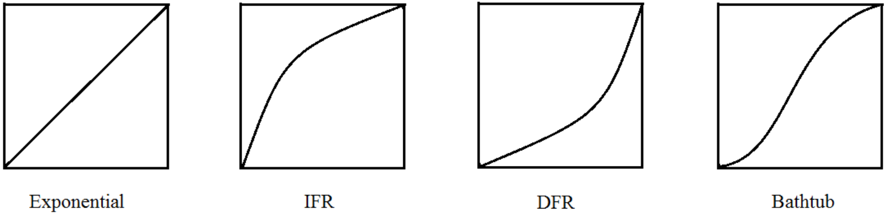
$$E(Y_i) = E(\mathcal{T}(T_{(i)})) = i\lambda \quad \text{for } i = 1, \ldots, n$$

so

$$E\left(\frac{Y_i}{Y_n}\right) \approx \frac{i\lambda}{n\lambda} = \frac{i}{n}$$

so the TTT-plot is approximately a plot of $(i/n, i/n)$ which are on a straight line.

SHAPES OF TTT-PLOTS

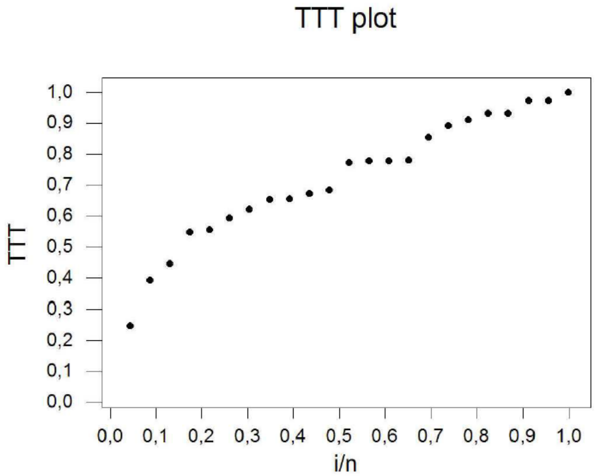


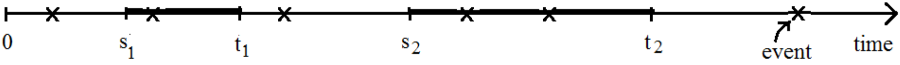
IFR: *Concave shape.* The first lifetimes are generally longer than expected from an exponential distribution, while the last ones are shorter.

DFR: *Convex shape.* The first lifetimes are generally shorter than expected from an exponential distribution, while the last ones are longer.

Bathtub: *S-shaped*, i.e. convex (DFR) in the beginning and concave (IFR) at the end.

BALL BEARINGS FAILURE DATA





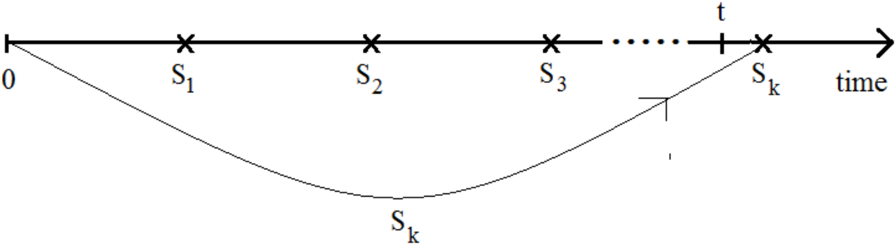
Definition: Let $N(s,t)$ = number of events in$(s,t]$

1. $P(N(t,t+h)=1)=\lambda h+o(h)\approx\lambda h$
2. $P(N(t,t+h)\geq 2)=o(h)\approx 0$
3. For disjoint intervals $(s_1,t_1]$, $(s_2,t_2],\ldots$, the counts $N(s_1,t_1],N(s_2,t_2],\ldots$ are independent random variables.

It can be shown that:

- $N(s,t)$ is Poisson $(\lambda(t-s))$ so $E[N(s,t)]=\lambda(t-s)$

λ is called the *intensity* of the process.



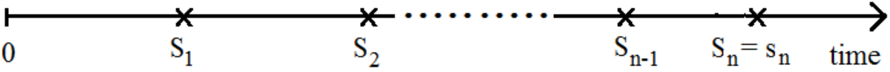
- Times between events are independent and distributed as expon(λ).
- The time to the kth event ($k = 1, 2, \ldots$) is *gamma-distributed* with pdf and reliability function given by, respectively,

$$f(t) = \frac{\lambda(\lambda t)^{k-1} e^{-kt}}{(k-1)!} \text{ for } t > 0$$

$$R(t) = P(S_k > t) =_{(*)} P(N(t) \leq k-1) = \sum_{x=0}^{k-1} \frac{(\lambda t)^x}{x!} e^{-\lambda t}$$

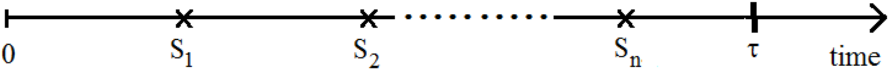
(*) See time point t in figure.

RESULT 1:

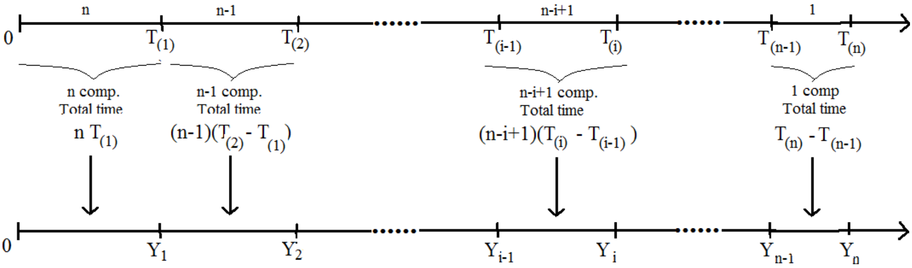


Let the HPP start at time $t = 0$ and continue until a given number n events have occurrred. Then, given the value $S_n = s_n$, the event times $S_1, \ldots, S_{n-1}$ are distributed as the ordering of $n-1$ i.i.d. variables from the distribution $U[0, s_n]$, i.e. the uniform distribution on the interval from 0 to s_n.

RESULT 2:

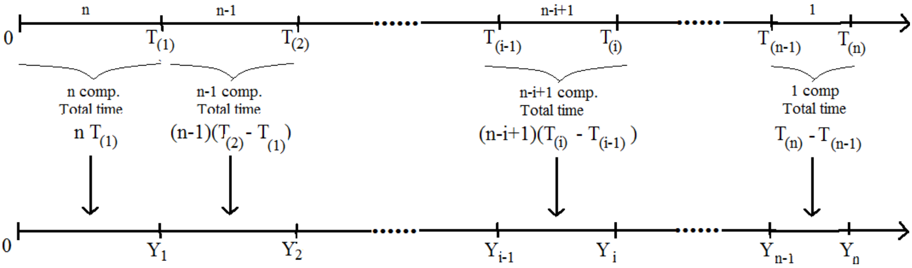


Let the HPP start at time $t = 0$ and continue until a given time τ. Let N denote the number of events that have occurrred until time τ (this is a random number). Then, given the value $N = n$, the event times $S_1, \ldots, S_n$ are distributed as the ordering of n i.i.d. variables from the distribution $U[0, \tau]$, i.e. the uniform distribution on the interval from 0 to τ.



Suppose $T_1, \ldots, T_n$ are distributed as expon(λ). Then $Y_1, Y_2, \ldots$ behaves like an HPP with intensity λ (called HPP(λ)), by result 5. By Result 1:

- Given the value $Y_n = y_n$, the $(Y_1, \ldots, Y_{n-1})$ are distributed as the ordering of $n-1$ i.i.d. $U[0, y_n]$.
- Hence, given the value $Y_n = y_n$, the $(Y_1/y_n, \ldots, Y_{n-1}/y_n)$ are distributed as the ordering of $n-1$ i.i.d. $U[0,1]$.
- Since the latter distribution does not depend on y_n, the $(Y_1/Y_n, \ldots, Y_{n-1}/Y_n)$ are distributed as the ordering of $n-1$ i.i.d. $U[0,1]$.



Recall: The $\left(\frac{Y_1}{Y_n}, \ldots, \frac{Y_{n-1}}{Y_n}\right)$ are distributed as the ordering of $n-1$ i.i.d. $U[0,1]$.

From this can be shown that we have, under exponentiality, exactly:

$$E\left(\frac{Y_i}{Y_n}\right) = \frac{i}{n}, \quad \text{for } i = 1, \ldots, n-1$$

while we plot:

$$\left(\frac{i}{n}, \frac{Y_i}{Y_n}\right), \quad \text{for } i = 1, \ldots, n$$

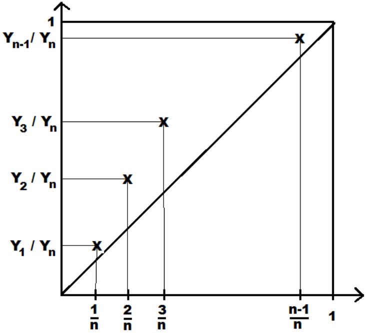
One is often not satisfied with just looking at *plots* to determine distributions. Assume we want to formally test

$$
\begin{aligned}
H_0 &\ : \ T \sim \text{expon}(\lambda) \text{ for some unspecified } \lambda \\
\textit{versus} \quad H_1 &\ : \ \textit{(either of)} \begin{cases} T & \text{has IFR} \\ T & \text{has DFR} \\ T & \text{has monotone failure rate} \end{cases}
\end{aligned}
$$

Suppose $T_1, \cdots, T_n$ is complete data set, i.e. no censorings.

The test statistic of Barlow-Proschan's test is

$$W = \frac{Y_1}{Y_n} + \frac{Y_2}{Y_n} + \cdot + \frac{Y_{n-1}}{Y_n} = \frac{\mathcal{T}(T_{(1)})}{\mathcal{T}(T_{(n)})} + \cdots + \frac{\mathcal{T}(T_{(n-1)})}{\mathcal{T}(T_{(n)})}$$



$$W = \frac{Y_1}{Y_n} + \frac{Y_2}{Y_n} + \cdot + \frac{Y_{n-1}}{Y_n}$$

When compared to the exponential distribution:

- W becomes "too large" if distribution is IFR
- W becomes "too small" if distribution is DFR

Thus: The null hypothesis H_0 of exponential distributon should be *rejected* if W is either much larger or much smaller than what should be expected from exponentially distributed lifetimes.

We therefore need the distribution of W when $T_1, \ldots, T_n \sim \text{expon}(\lambda)$. We know already:

$$\frac{Y_1}{Y_n}, \cdots, \frac{Y_{n-1}}{Y_n}$$

are distributed as the ordering of $n-1$ independent $U[0,1]$-variables, so:

- $W =$ sum of $n-1$ independent $U[0,1]$-variables
- $E(W) = (n-1)/2$
- $Var(W) = (n-1)/12$

Thus by the Central Limit Theorem, W is approximately normal:

$$W \approx N\left(\frac{n-1}{2}, \frac{n-1}{12}\right) \textit{ when lifetimes are exponential}$$

Recall:

$$W = \frac{Y_1}{Y_n} + \frac{Y_2}{Y_n} + \cdots + \frac{Y_{n-1}}{Y_n} \approx N(\frac{n-1}{2}, \frac{n-1}{12})$$

Thus we compute

$$Z = \frac{W - \frac{n-1}{2}}{\sqrt{\frac{n-1}{12}}}$$

which is $\approx N(0,1)$ under H_0.

Tests with level α: Let $T_1, \cdots, T_n$ be a complete sample of T.

$$H_0 : T \sim \text{expon}(\lambda)$$

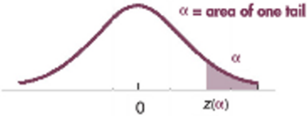
$$\textit{versus } H_1 : \begin{cases} T \text{ is IFR : Reject if } Z \geq z_\alpha \\ T \text{ is DFR: Reject if } Z \leq -z_\alpha \\ T \text{ has monotone hazard: Reject if } Z \leq -z_{\alpha/2} \text{ or } Z \geq z_{\alpha/2} \end{cases}$$

TABLE 4

Critical Values of Standard Normal Distribution

A ONE-TAILED SITUATIONS

The entries in this table are the critical values for z for which the area under the curve representing α is in the right-hand tail. Critical values for the left-hand tail are found by symmetry.

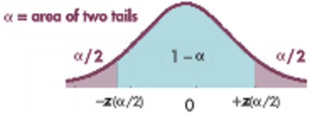


	Amount of α in one tail						
α	0.25	0.10	0.05	0.025	0.02	0.01	0.005
$z(\alpha)$	0.67	1.28	1.65	1.96	2.05	2.33	2.58

One-tailed example:
$\alpha = 0.05$
$z(\alpha) = z(0.05) = 1.65$

B TWO-TAILED SITUATIONS

The entries in this table are the critical values for z for which the area under the curve representing α is split equally between the two tails.



	Amount of α in two tails					
α	0.25	0.20	0.10	0.05	0.02	0.01
$z(\alpha/2)$	1.15	1.28	1.65	1.96	2.33	2.58
$1-\alpha$	0.75	0.80	0.90	0.95	0.98	0.99
	Area in the "center"					

Two-tailed example:
$\alpha = 0.05$ or $1 - \alpha = 0.95$
$\alpha/2 = 0.025$
$z(\alpha/2) = z(0.025) = 1.96$

EXAMPLE: BARLOW-PROSCHAN'S TEST

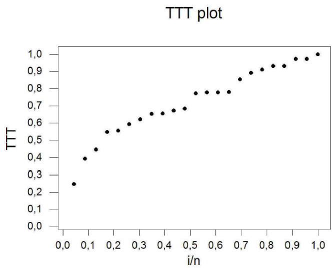
Row	Time	TTT interval	TTT cum	i/n	TTT
1	6,3	10*6,3 = 63,0	63,0	0,1	0,05943
2	11,0	9*4,7 = 42,3	105,3	0,2	0,09934
3	21,5	8*10,5 = 84,0	189,3	0,3	0,17858
4	48,4	7*27,9 = 188,3	377,6	0,4	0,35623
5	90,1	6*41,7 = 250,2	627,8	0,5	0,59226
6	120,2	5*30,1 = 150,5	778,3	0,6	0,73425
7	163,0	4*42,8 = 171,2	949,5	0,7	0,89575
8	182,5	3*19,5 = 58,5	1008,0	0,8	0,95094
9	198,0	2*15,5 = 31,0	1039,0	0,9	0,98019
10	219,0	1*21,0 = 21,0	1060,0	1,0	1,00000

Here W is the sum of the last column, except the last "1". We have $W = 4.847$ and

$$Z = \frac{4.847 - \frac{9}{2}}{\sqrt{\frac{9}{2}}} = 0.401$$

so we do not reject at $\alpha = 0.05$, for example.

BALL BEARINGS FAILURE DATA

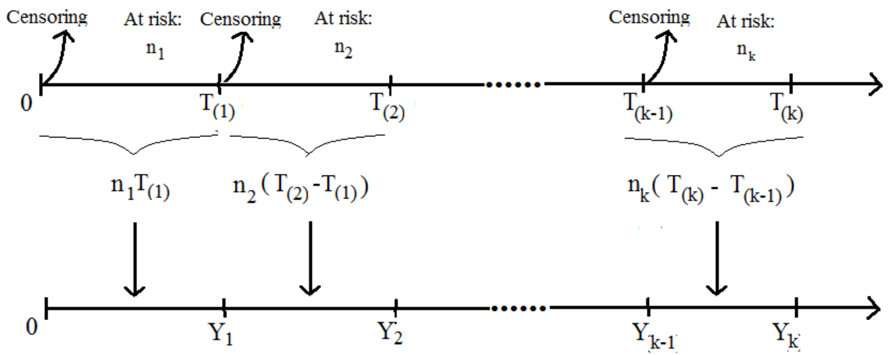


Use of Macro from course web page: $W = 15.648$, $n = 23$, so

$$Z = \frac{15.648 - 11}{\sqrt{\frac{22}{12}}} = 3.4328$$

and we **reject** (at any reasonable significance level) a test of

H_0 : exponential distribution *versus* H_1 : IFR distribution.



Let $T_{(1)} < T_{(2)} < \cdots < T_{(k)}$ be the observed *failure* times.

Assume that the censored observations are always deleted from the data in the immediate beginning of each interval $(T_{(i-1)}, T_{(i)})$, and let n_i be the number at risk after deletion of the censored ones.

Then $Y_1, Y_2, \ldots$ is still a HPP when lifetimes are exponential.

TTT-PLOT FOR CENSORED DATA (CONT.)

On the previous slide, the censored observations contribute to the Total Time on Test only in the intervals strictly before the ones where they are censored.

An improvement of the method is to let the censored observations contribute also in the interval where they are censored, but only up to the time they are censored.

This means in practice that we compute the TTT as for the noncensored case, but we let *only the* **failure times** *be recorded as the event times* $Y_1, \ldots, Y_k$, and we plot

$$\left(\frac{i}{k}, \frac{Y_i}{Y_k}\right), \quad \text{for } i = 1, \ldots, k$$

Row	Time	Censor	No at risk	Total time	Cum total time	Plot total time
1	31,7	1	16	507,2	507,2	507,2
2	39,2	1	15	112,5	619,7	619,7
3	57,5	1	14	256,2	875,9	875,9
4	65,0	0	13	97,5	973,4	983,0
5	65,8	1	12	9,6	983,0	1029,2
6	70,0	1	11	46,2	1029,2	1274,3
7	75,0	0	10	50,0	1079,2	1286,1
8	75,2	0	9	1,8	1081,0	
9	87,5	0	8	98,4	1179,4	
10	88,3	0	7	5,6	1185,0	
11	94,2	0	6	35,4	1220,4	
12	101,7	0	5	37,5	1257,9	
13	105,8	1	4	16,4	1274,3	
14	109,2	0	3	10,2	1284,5	
15	110,0	1	2	1,6	1286,1	
16	130,0	0	1	20,0	1306,1	

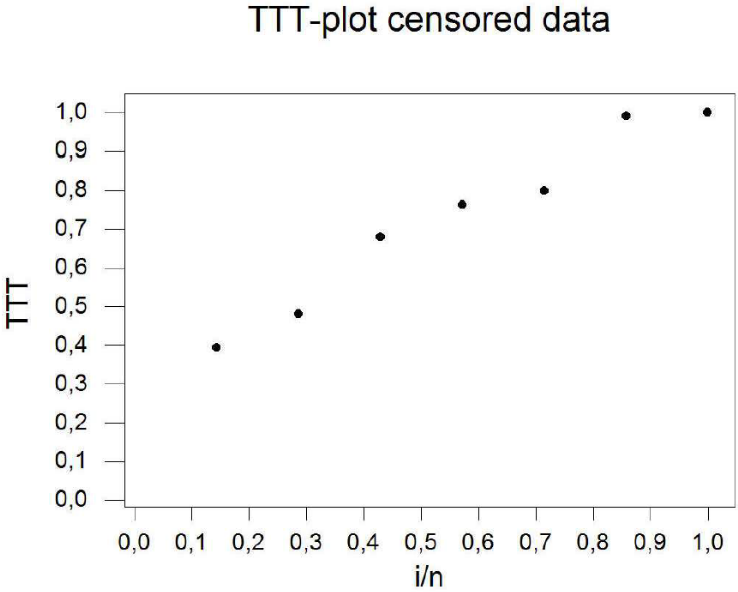
Row	i/n	TTT
1	0,14286	0,39437
2	0,28571	0,48184
3	0,42857	0,68105
4	0,57143	0,76433
5	0,71429	0,80025
6	0,85714	0,99082
7	1,00000	1,00000

Data from Table 11.1/9.3

BARLOW-PROSCHAN'S TEST:

W = 0.39+0.48+0.68+0.76+0.80+0.99 =
= 4.10 (k-1 = 6)

EXAMPLE: TTT-PLOT FOR CENSORED DATA



Assume first two groups:

Group 1: Control group, lifetime T_1, with $R_1(t) = P(T_1 > t)$

Group 2: Treatment group, lifetime T_2, with $R_2(t) = P(T_2 > t)$

Want to test:

$$H_0 : R_1(t) = R_2(t) \quad \text{for all} \quad t$$

(i.e. *no* difference between groups)

$$\text{vs } H_1 : R_1(t) \neq R_2(t) \text{ for at least one } t$$

Graphical solution: Look at *KM-Plots*

Comparing two groups:

6-Mercaptopurine in Acute Leukemia

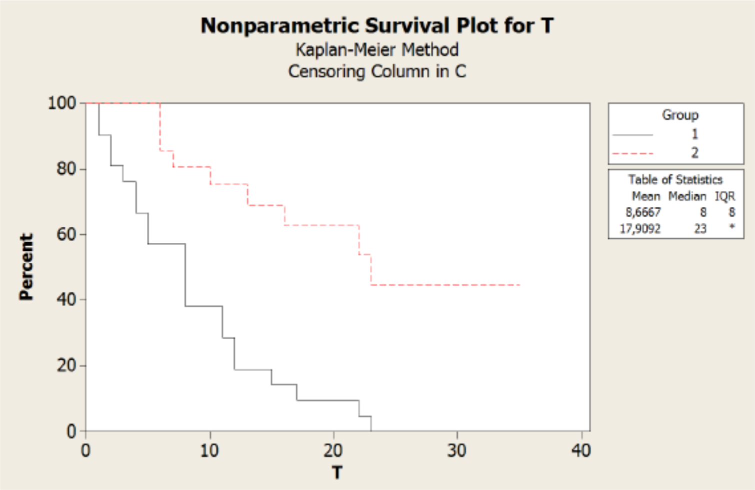
The 6-Mercaptopurine in Acute Leukemia trial

- Conducted in 1959-1960
- Patients had undergone corticosteroid therapy for acute leukemia
- 6-Mercaptopurine versus placebo
- Outcome: length of complete remission (weeks)
- Subjects entered in pairs and followed until at least one member of each pair relapsed.
- Stopped after 21 pairs of subjects were entered

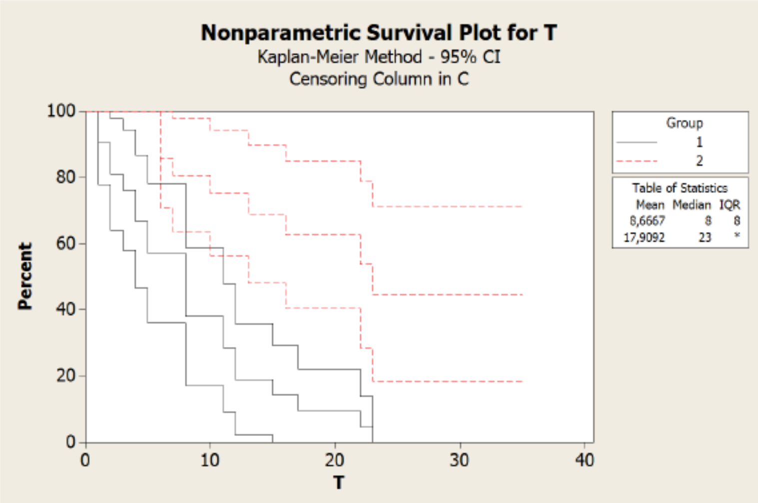
Outcomes ("+"=censored):

- 6-MP: 6+, 6, 6, 6, 7, 9+, 10+, 10, 11+, 13, 16, 17+, 19+, 20+, 22, 23, 25+, 32+, 32+, 34+, 35+
- Placebo: 1, 1, 2, 2, 3, 4, 4, 5, 5, 8, 8, 8, 8, 11, 11, 12, 12, 15, 17, 22, 23

Group 1=Placebo (control), Group 2=6MP



Group 1=Placebo (control), Group 2=6MP (with 95% confidence intervals)



FORMAL TESTING OF $H_0: R_1(t) \equiv R_2(t)$

Formal testing can be done by

- The Logrank Test
- Mantel-Haenszel Test

A simple version is to compute a χ^2-statistic of the form

$$V = \frac{(O_1 - E_1)^2}{E} + \frac{(O_2 - E_2)^2}{E_2}$$

where

- O_1, O_2 are *observed* # failures of the two groups
- E_1, E_2 are *expected* # failures **if** the survival functions are equal.
- Note that $O_1 + O_2 =$ total number of failures $= E_1 + E_2$.

Under H_0 is $V \approx \chi^2_1$ (i.e. χ^2-distributed with 1 degree of freedom)

Go through all *failure times* $T_{(1)}, \cdots, T_{(k)}$ considering groups together:

	Group 1	Group 2	Total at $T_{(j)}$
# at risk:	N_{1j}	N_{2j}	N_j
Obs # fail at $T_{(j)}$	O_{1j}	O_{2j}	O_j
Est prob of fail under H_0	$\frac{O_j}{N_j}$	$\frac{O_j}{N_j}$	
Estim exp # failures	$E_{1j} = \frac{O_j}{N_j} \cdot N_{1j}$	$E_{2j} = \frac{O_j}{N_j} \cdot N_{2j}$	

Then sum over all failure times $T_{(1)}, \cdots, T_{(k)}$:

$$O_1 = \sum_{j=1}^{k} O_{1j}, \; E_1 = \sum_{j=1}^{k} E_{1j}$$

$$O_2 = \sum_{j=1}^{k} O_{2j}, \; E_2 = \sum_{j=1}^{k} E_{2j}$$

If more than two groups are compared, the table and the test statistic are extended in a natural way, while the degrees of freedom of the χ^2-distribution equals # groups minus 1.

C = Control group (Placebo)

B = Treatment group (6MP)

Time	RiskC	RiskB	Risk	FailC	FailB	Fail	EC	EB
1	21	21	42	2	0	2	(2/42)*21 = 1	(2/42)*21 = 1
2	19	21	40	2	0	2	(2/40)*19 = 0.95	(2/40)*21 = 1.05
3	17	21	38	1	0	1	(1/38)*17 = 0.447	(1/38)*21 = 0.553
4	16	21	37	2	0	2	(2/37)*16 = 0.865	(2/37)*21 = 1.135
13	4	12	16	0	1	1	(1/16)*4 = 0.25	(1/16)*12 = 0.75
23	1	6	7	1	1	2	(2/7)*1 = 0.286	(2/7)*6 = 1.714
Total				21	9		10.749	19.251

Test statistic:

$$\frac{(O_C - E_C)^2}{E_C} + \frac{(O_B - E_B)^2}{E_B}$$

$$= \frac{(21-10.749)^2}{10.749} + \frac{(9-19.251)^2}{19.251} = 5.46 + 9.77 = 15.33$$