Contents

- Compare survival distributions
  - Comparison of treatments
  - Comparison of groups
    - (M or F)
- Non-parametric
  - Compare K-M plots; Logrank tests
- Parametric
  - MLE and Likelihood Ratio tests

- Log-rank test for two samples
  - Compares 'observed' and 'expected' numbers of deaths in the two samples
    - 'expected' calculated by sharing the next death between the groups in proportion to numbers at risk in each group
    - i.e. assuming no difference in risk factors between the groups

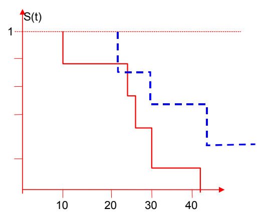
- **Example**

12 patients, 2 treatments,
survival times (weeks)

Group 1: 10 26 28 30 41 12*
Group 2: 24 30 42 15* 40* 42*

(* denotes censored)

- Step 1: K-M Plots



- Step 2: calculate 'expected' numbers
  - Order times
    10,12*,15*,24,26,28,30,30,40*,41,42,42*
  - First death at t=10,
    - 6 in each group at that time so expect $1\times{}^6/_{12}$ of this death to be in group 1 and $1\times{}^6/_{12}$ in group 2.
  - Next death at t=24:
    - 4 in gp 1 and 5 in gp 2 so expect $1\times{}^4/_9$ in gp 1 and $1\times{}^5/_9$ in gp 2
    - (note two censorings before t=24)

		Number at risk			Number of deaths			Expected no. of deaths	
i	$t_{(i)}$	r_{1i}	r_{2i}	r_i	d_{1i}	d_{2i}	d_i	e_{1i}	e_{2i}
1	10	6	6	12	1	0	1	1/2	1/2
2	24	4	5	9	0	1	1	4/9	5/9
3	26	4	4	8	1	0	1	1/2	1/2
4	28	3	4	7	1	0	1	3/7	4/7
5	30	2	4	6	1	1	2	2/3	4/3
6	41	1	2	3	1	0	1	1/3	2/3
7	42	0	2	2	0	1	1	0	1
					O_1=5	O_2=3		E_1=2.87	E_2=5.13

- Sum obs & exp for each group O_i and E_i
- Calculate logrank statistic: $(O_1–E_1)^2/E_1 + (O_2–E_2)^2/E_2 \sim \chi^2_1$ if no difference in risk between two groups
- Here =2.46 < $\chi^2_{1;0.95}$ = 3.84
  - **i.e. no significant difference in survivor functions at 5% level**

- **Notes**
  - Obvious generalization to k groups and then χ^2 has k–1 df
  - other nonparametric tests available —
    - Gehan
    - CoxMantel
    - Peto and Peto
    - MantelHaenszel etc.
  - See references and computer packages.

- Available in Minitab
  - option in Kaplan-Meier plot
    - Click ***By variable*** and alter default choice in ***Results***
- Available in SPSS
  - option in Kaplan-Meier plot
    - Click ***Factor*** and ***Compare Factor***
- NB package results adjust for different variances so results slightly different
  - (c.f. M-H test)

- In **R** need command **`survdiff()`**:

```
> library(survival)
   Loading required package: splines
> load("braintu.Rdata")
> attach(braintu)
> brain.sv<-Surv(time, censor)
> survdiff(brain.sv ~ group)
```

Note capitalisation


```
> survdiff(brain.sv ~ group)
Call:
survdiff(formula = brain.sv, data = braintu)
        N Observed Expected (O-E)^2/E (O-E)^2/V
group=1 6        5     2.87     1.575      2.88
group=2 6        3     5.13     0.882      2.88
 Chisq= 2.9  on 1 degrees of freedom, p= 0.0896
```

- **i.e. no significant difference in survivor functions at 5% level**

- Note χ^2 value calculated by hand was 2.46 (slide 104) difference is because of presence of ties & **R** applies an adjustment to allow for these

- **Parametric Tests**
  - Normal approxs for MLEs
  - Asymptotic χ^2 for LR tests
- MLE test:
  - Estimate parameters by ML for each group
  - Get s.e. of estimates from general theory
  - Two sample Normal test

- If θ_i is [single] parameter then test uses

$$\frac{\hat{\theta}_1 - \hat{\theta}_2}{\sqrt{[\text{s.e.}(\hat{\theta}_1)]^2 + [\text{s.e.}(\hat{\theta}_2)]^2}} \sim N(0,1)$$

- e.g. example above (assume exponential):
  n_1=6, $\Sigma\delta_i$=5, Σt_i=147, $\hat{\lambda}_1$ = 5/147 = 0.034
  and var($\hat{\lambda}_1$) = 0.034²/5 = 0.0002312
  n_2=6, $\Sigma\delta_i$=3, Σt_i=193, $\hat{\lambda}_2$ = 3/193 = 0.0155
  and var($\hat{\lambda}_2$) = 0.0155²/3 = 0.00008
- Test statistic = (0.034 – 0.0155)/.0177
  =1.02 < 1.96
- **so no evidence at 5% level of difference in survival times**

- **Likelihood Ratio Test**
  - if θ_i is a parameter then
    - 1: Maximize likelihood L(θ_i) separately for each sample wrt θ_i and add together
    - 2: treat both samples as one big sample and maximize likelihood wrt this single value of θ
    - 3: take 2 x difference in logs of max likelihoods
    - 4: compare with χ^2 with d.f.= dimension (θ)
    - **If [improbably] big then evidence of difference between samples**

- Example: exponential
  - $f(t) = \lambda e^{-\lambda t}$ $S(t) = e^{-\lambda t}$
  - Likelihood $L(\lambda) = \lambda^D e^{-\lambda T}$
    - (D = #deaths = $\Sigma\delta_i$, T = total times observed = Σt_i)
  - MLE of λ = D/T
  - $\text{Log}(L_{max}) = D\log(D/T) - D$

- Total of max logliks for 2 samples is
  $D_1\log(D_1/T_1) - D_1 + D_2\log(D_2/T_2) - D_2$
- MLE if 2 samples combined is
  $(D_1+D_2)/(T_1+T_2)$
- Difference in max-liks is
  $D_1\log(D_1/T_1) + D_2\log(D_2/T_2) -$
  $(D_1+D_2)\log\{(D_1+D_2)/(T_1+T_2)\}$

- Example
  - n_1=6, $D_1 = \Sigma\delta_i = 5$, $T_1 = \Sigma t_i = 147$
  - n_1=6, $D_2 = \Sigma\delta_i = 3$, $T_2 = \Sigma t_i = 193$
  - Test statistic is
    2{5log(5/147)+3log(3/193)
    –(5+3)log(5+3)/(147+193)}
    = 1.198 < $\chi^2_{1;0.95}$ = 3.84
    - **so no evidence at 5% level of difference in survival**

- Notes
  - LR test extends to k groups
  - For two groups MLE & LR tests asymp. equiv.
  - LR test better for small samples
  - For large samples logrank test as powerful as parametric tests (& is safer)
  - Logrank test designed for alternatives with ***proportional hazards***
    - i.e. '*works best*' with proportional hazards (see later)
  - Implementation in **R** (see notes 3.4.1)
    - Calculations for MLE test for exponential distributions can be done in R
    - MLE and LR tests for all distributions can be done using **`survreg()`** — see next section

- **Basic calculations in R for exponential**

```
> library(survival)
> load("braintu.Rdata")
> attach(braintu)
> sum(time[group==1]); sum(time[group==2])
[1] 147
[1] 193
> sum(censor[group==1]);
  sum(censor[group==2])
[1] 5
[1] 3
```


- **Basic calculations in R for exponential**

```
> brain.sv<-Surv(time,censor)
> brain.regexp<-survreg(brain.sv~group,
  dist="exponential")
> summary(brain.regexp)
Call:
survreg(formula = brain.sv ~ group, dist =
  "exponential")
              Value Std. Error    z        p
(Intercept) 3.381      0.447 7.56 4.03e-14
group2      0.783      0.730 1.07 2.84e-01
Scale fixed at 1
Exponential distribution
Loglik(model)= -37.4   Loglik(intercept only)= -38
Chisq= 1.2 on 1 degrees of freedom, p= 0.27
Number of Newton-Raphson Iterations: 4
```


- **Basic calculations in R for exponential**

```
Value        Std. Error    z        p
(Intercept) 3.381      0.447 7.56 4.03e-14
group2      0.783      0.730 1.07 2.84e-01
```

1/exp(3.831) = 0.034 = $\hat{\lambda}_1$

1/exp({3.831+0.783) = 0.155 = $\hat{\lambda}_2$

p-value for test of equality of groups

```
Chisq= 1.2 on 1 degrees of freedom, p= 0.27
Number of Newton-Raphson Iterations: 4
```

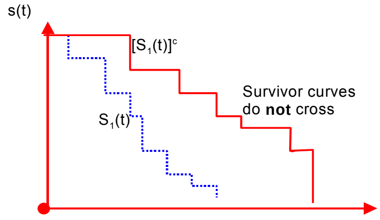
LRT Statistic assuming exponential model

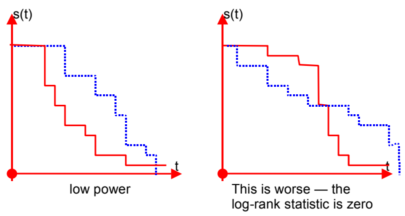
- **Proportional Hazards**
  - Logrank test works best when

    $h_2(t)=ch_1(t)$

    i.e. when $S_2(t)=[S_1(t)]^c$

    If not then test has *low power*





- **Summary**
  - **Logrank test** two (or more groups)
    - Based on $(O–E)^2/E \sim \chi^2_{k-1}$
    - Similar calculations to Kaplan-Meier which should be a preliminary step
    - Packages may give slightly different answers because of using $(O–E)^2/\text{var}(E)$
    - Best when proportional hazards

- **Summary (ctd)**
  - **M.L.E. Test** (2 groups, single parameter)
  - Based on twosample Normal test with s.e.s from general ML theory
  - **Likelihood Ratio Test**
    - k groups, any # of parameters
    - Difference in sum of separate max likelihoods and pooled max likelihood