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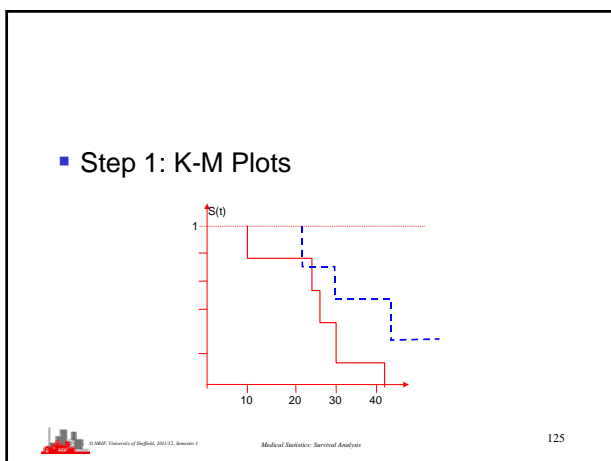
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- Compare survival distributions
 - ◆ Comparison of treatments
 - ◆ Comparison of groups
 - (M or F)
 - Non-parametric
 - ◆ Compare K-M plots; Log-rank tests
 - Parametric
 - ◆ MLE and Likelihood Ratio tests
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- 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
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- **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)
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- 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 $1 \times \frac{6}{12}$ of this death to be in group 1 and $1 \times \frac{6}{12}$ in group 2.
 - ◆ Next death at t=24:
 - 4 in gp 1 and 5 in gp 2 so expect $1 \times \frac{4}{9}$ in gp 1 and $1 \times \frac{5}{9}$ in gp 2
 - (note two censorings before t=24)
- 
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i	t ₀	Number at risk			Number of deaths			Expected no. of deaths	
		r _{1i}	r _{2i}	r _i	d _{1i}	d _{2i}	d	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 log-rank 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 non-parametric tests available —
 - Gehan
 - Cox-Mantel
 - Peto and Peto
 - Mantel-Haenszel 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




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- If θ_i is [single] parameter then test uses

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



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- ◆ e.g. example above (assume exponential):
 - $n_1=6, \Sigma \delta_i=5, \Sigma t_i=147, \hat{\lambda}_1 = 5/147 = 0.034$
 - and $\text{var}(\hat{\lambda}_1) = 0.034^2/5 = 0.0002312$
 - $n_2=6, \Sigma \delta_i=3, \Sigma t_i=193, \hat{\lambda}_2 = 3/193 = 0.0155$
 - and $\text{var}(\hat{\lambda}_2) = 0.0155^2/3 = 0.00008$
- ◆ Test statistic = $(0.034 - 0.0155)/0.0177 = 1.02 < 1.96$
- ◆ **so no evidence at 5% level of difference in survival times**




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- **Likelihood Ratio Test**
 - ◆ if θ_i is a parameter then
 - 1: Maximize likelihood $L(\theta_i)$ 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**




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



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



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Example

- $n_1=6, D_1 = \sum \delta_i = 5, T_1 = \sum t_i = 147$
- $n_2=6, D_2 = \sum \delta_i = 3, T_2 = \sum t_i = 193$
- Test statistic is

$$2\{5\log(5/147)+3\log(3/193) - (5+3)\log(5+3)/(147+193)\}$$

$$= 1.198 < \chi^2_{1;0.95} = 3.84$$
 - so no evidence at 5% level of difference in survival

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Notes

- LR test extends to k groups
- For two groups MLE & LR tests asymp. equiv.
- LR test better for small samples
- For large samples log-rank test as powerful as parametric tests (& is safer)
- Log-rank 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

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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
    
```

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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
    
```

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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

$1/\exp(3.831) = 0.034 = \hat{\lambda}_1$
 $1/\exp\{3.831+0.783\} = 0.155 = \hat{\lambda}_2$
 Chisq= 1.2 on 1 degrees of freedom, p= 0.27
 Number of Newton-Raphson Iterations: 4
 LRT Statistic assuming exponential model

p-value for test of equality of groups

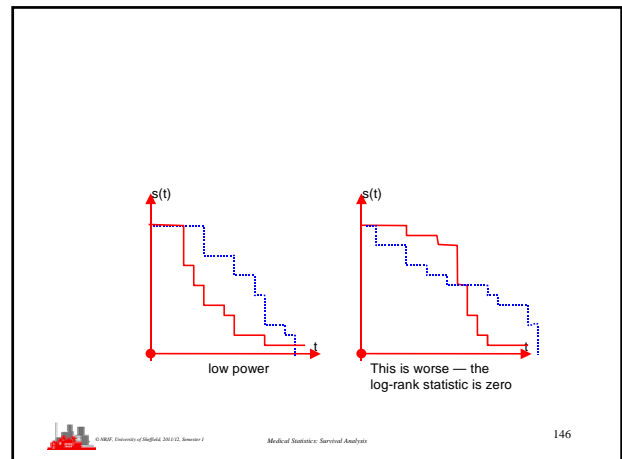
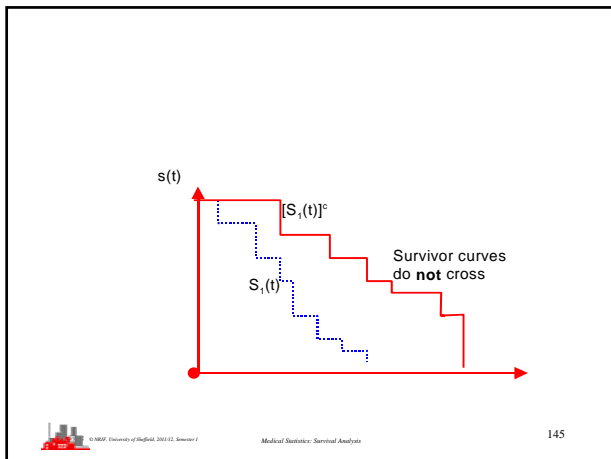
Proportional Hazards

- Log-rank 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*

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- **Summary**
 - ♦ **Log-rank 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 two-sample 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

