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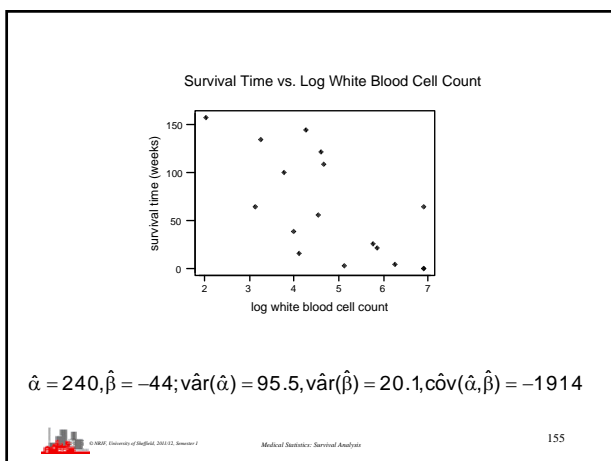
- Individual hazard rate $h_i(t)$
 - e.g. $T_i \sim \text{Ex}(\lambda_i)$ with $f_i(t) = \lambda_i e^{-\lambda_i t}$
 - could estimate λ_i individually
 - Better: link λ_i together – fewer parameters
 - e.g. $E[T_i] = \lambda_i^{-1} = \alpha + \beta x_i$
 - (exponential regression)
 - (c.f. Normal regression)

- Estimate α & β by ML – standard theory
 - Construct likelihood by $f(t_i)$ for uncensored and $S(t_i)$ for censored observations
 - Get estimates and CI for λ_i from α & β
 - Strictly need condition $\alpha + \beta x_i > 0$ (since $\lambda_i > 0$)

Example

myelogenous leukemia survival times with covariate white blood cell count

Patient	(AG positive) n=17	
	WBC $\times 10^2$	Survival Time (weeks)
1	23	65
2	7.5	156
3	43	100
4	26	134
5	60	16
6	105	108
7	100	121
8	170	4
9	54	39
10	70	143
11	94	56
12	320	26
13	350	22
14	1000	1
15	1000	1
16	520	1
17	1000	5
Median values	100	56



- Minitab implementation
- Stat>Reliability/Survival> Regression with Life Data
 - Actually models $\log(\text{survival})$ so different answers [slightly] from above
- Similarly S-Plus and R, details in notes



Two-Sample Example

- ◆ $h_1(t)=\lambda_1$ and $h_2(t)=\lambda_2$
- ◆ Define dummy variable
0 for group 1, 1 for group 2
- ◆ $h(t;x) = \lambda e^{\beta x} = \lambda$ for $x=0$ (group 1)
or $= \lambda e^{\beta}$ for $x=1$ (group 2)
- ◆ The sign of β determines whether
 $\lambda_2 > \lambda_1$ ($\beta > 0$) or $\lambda_1 > \lambda_2$ ($\beta < 0$)



Notes

- ◆ $\log_e h(t;x) = \log_e(\lambda) + \beta x$
i.e. *log-linear model* for hazard function
- ◆ guarantees $h(t;x) > 0$
- ◆ extend to several groups with $h(t;x) = \lambda e^{\beta'x}$
- ◆ Could let \underline{x} be any vector of
 - covariates
 - prognostic factors




- ◆ allowing for covariates gives more sensitive tests
- ◆ can correct for imbalance in initial randomization
- ◆ incorporating prognostic factors for investigating factors in their own right
- ◆ can investigate **interactions**
 - see later re interactions
 - see later for implementation **R** of parametric and non-parametric models



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- Generally model $h(t) \rightarrow h(t;\underline{x}) = h_0(t) \exp\{\beta'\underline{x}\}$ where $h_0(t)$ is the 'underlying' hazard rate
 - ♦ β_j reflects the effect of x_j on survival
 - if $\beta_j > 0$: $x_j \nearrow \Rightarrow$ hazard $\nearrow \Rightarrow$ survival prospect \searrow
 - if $\beta_j < 0$: $x_j \nearrow \Rightarrow$ hazard $\searrow \Rightarrow$ survival prospect \nearrow
 - if $\beta_j = 0$: $x_j \Rightarrow$ no effect on survival.




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- **Exponential Model**
 - ♦ $h(t;\underline{x}) = \lambda \exp\{\beta'\underline{x}\}$
 - $f(t;\underline{x}) = \lambda \exp\{\beta'\underline{x}\} \exp\{-\lambda t \exp\{\beta'\underline{x}\}\}$
 - $S(t;\underline{x}) = \exp\{-\lambda t \exp\{\beta'\underline{x}\}\}$
- **Weibull Model**
 - ♦ $h(t;\underline{x}) = \lambda \gamma t^{\gamma-1} \exp\{\beta'\underline{x}\}$.
- Estimation by [numerical] ML




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- **Proportional Hazards Model**
 - ♦ semi-parametric model [Cox, 1972]
 - ♦ $h(t;\underline{x}) = h_0(t) \exp\{\beta'\underline{x}\}$
 - ♦ $h_0(t)$ — baseline hazard
 - i.e. hazard of a patient with $\underline{x}=\underline{0}$
 - ♦ Useful for investigating prognostic factors when actual survival distribution not of immediate interest.




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- $h(t;\underline{x}) = h_0(t) \exp\{\beta'\underline{x}\}$
 - ♦ Dependence on factors and covariates is precisely modelled
 - ♦ Distribution of failure not specified
 - $h_0(t)$ is not specified
 - ♦ Useful in medical situations
 - important to know which prognostic variables have an effect and to what extent




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- Can give answers such as
 - ♦ Treatment halves hazard rate
 - ♦ Smoking trebles hazard rate
- But not answers such as
 - ♦ Red wine increases survival by 10 years
 - ♦ Coffee shortens life by 6 months




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- **special cases**
 - ◆ Exponential
 - $h(t; \underline{x}) = \lambda \cdot \exp\{\beta' \underline{x}\}$
 - $h_0(t) = \lambda$
 - ◆ Weibull
 - $h(t; \underline{x}) = \lambda \gamma t^{\gamma-1} \exp\{\beta' \underline{x}\}$
 - $h_0(t) = \lambda \gamma t^{\gamma-1}$

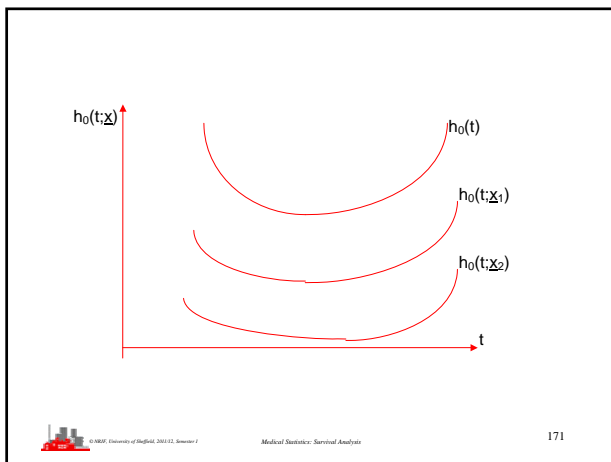


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- patients with covariates \underline{x}_1 and \underline{x}_2
 - $h(t; \underline{x}_1) / h(t; \underline{x}_2) = h_0(t) \exp\{\beta' \underline{x}_1\} / h_0(t) \exp\{\beta' \underline{x}_2\}$
 - $= \exp\{\beta' (\underline{x}_1 - \underline{x}_2)\}$
- ◆ **Independent of t**
- ◆ hazard functions proportional over time
- ◆ linear component does not vary with time



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- Patients have the same 'shape' of hazard function
 - but shifted multiplicatively according to \underline{x} .
- **Hazard functions can never cross**
 - ◆ Preliminary check on K-M estimates
 - ◆ Proportional hazard models are not appropriate if K-M estimates clearly cross




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- **Parameter Estimation**
 - ◆ Observations
 - Survival times t_1, t_2, \dots, t_n
 - Censorings $\delta_1, \delta_2, \dots, \delta_n$
 - Covariates $\underline{x}_1, \underline{x}_2, \dots, \underline{x}_n$
 - ◆ likelihood $= \prod_{i=1}^n [h(t_i; \underline{x}_i)]^{\delta_i} S(t_i; \underline{x}_i)$
 - ◆ $S(t; \underline{x}_i) = [S_0(t; \underline{x}_i)] \exp\{\beta' \underline{x}_i\}$



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- Cannot maximize this without $h_0(t)$
- Instead use **partial likelihood**
 - ◆ Consider time points at which deaths occur and $P[\text{individual } i \text{ dies at time } t_{(i)}]$
 - ◆ Construct likelihood from this by a combinatorial argument



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◆ P[it is individual i who dies at time $t_{(i)}$]

$$= \frac{h_0(t_{(i)})e^{\beta'x_{(i)}}}{\sum_{j \in R(t_{(i)})} h_0(t_{(i)})e^{\beta'x_{(j)}}}$$

$$= \frac{e^{\beta'x_{(i)}}}{\sum_{j \in R(t_{(i)})} e^{\beta'x_{(j)}}$$

◆ by proportional hazards assumption




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■ And then obtain partial likelihood

$$L(\beta) = \prod_{i=1}^n \left\{ \frac{e^{\beta'x_{(i)}}}{\sum_{j \in R(t_{(i)})} e^{\beta'x_{(j)}} \right\}^{\delta_{(i)}}$$


■ maximize this w.r.t. β



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■ Notes

- ◆ If no censored observations this is a **conditional** likelihood
 - conditional on the observed $t_{(1)}, t_{(2)}, \dots, t_{(n)}$
- ◆ With censored observations this is known as a **partial** likelihood
- ◆ Cox (1975) showed that the usual likelihood methods apply in this case
 - Also known as **Cox Regression**



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- ◆ Asymptotic normality
- ◆ Asymptotic variance on second partial derivative of log-likelihood
 - i.e. treat partial likelihood just as if it was a full likelihood
- ◆ Various adjustments for ties etc.



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■ Example


Variable	Coefficient	Standard Error	χ^2 statistic (using lrt)	coeff/s.e
treatment (0=A, 1=B)	-1.42	0.64	4.89	-2.22
age (years)	-0.004	0.034	0.01	-0.12
sex (1=M, 0=F)	0.31	0.72	0.18	0.43
volume of heart (mm)	0.0076	0.0036	4.44	2.11
Duration of symptoms (months)	-0.004	0.063	0.00	-0.06
digitalisation	-0.59	0.73	0.66	-0.81



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■ Can use χ^2 statistic or coeff/s.e.


- ◆ χ^2 statistic if factor with > 2 levels
- ◆ coeff/s.e. if factor with only 2 levels or continuous covariate
 - then $\chi^2 = (\text{coeff/s.e.})^2$ for one coefficient
 - [continuous covariate of binary factor]
 - $\chi^2 = \sum (\text{coeff/s.e.})^2$ over the k-1 dummy variables
 - k-level factor



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- Treatment:
 - ◆ $|-2.22| > 1.96$
 - ◆ Good evidence of effect of treatment
 - ◆ Coeff < 0 so treatment = 1 decreases hazard, i.e. treatment B is 'better'
- Heart volume:
 - ◆ coeff/s.e. = $+2.11 > 1.96$
 - ◆ Increased heart volume decreases relapse time



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- No evidence that other factors affect relapse time
- **NB Not shown that other factors have no effect**
- Useful to calculate CIs:
 - ◆ 95% CI for β_3 (M/F) is $0.31 \pm 2 \times 0.72 = (-1.13, 1.75)$
 - i.e. could be large difference between M & F



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Interpretation of β

- Consider model $h(t; \underline{x}) = h_0(t) \exp\{\beta' \underline{x}\}$
 $= h_0(t) \exp\{\beta_1 x_1 + \beta_2 x_2 + \dots + \beta_k x_k\}$
 - where x_1 is a factor indicating treatment (say)
 - $x_1=1$ for treatment, $x_1=0$ for placebo
- ◆ hazard for those on treatment is $h_0(t) \exp\{\beta_1 + \beta_2 x_2 + \dots + \beta_k x_k\}$ &
 $h_0(t) \exp\{\beta_2 x_2 + \dots + \beta_k x_k\}$ on placebo
- ◆ So **hazard ratio** for treatment is $\exp\{\beta_1\}$
 - So of interest to estimate $\exp\{\beta_1\}$ [&/or β_1]
 - With confidence intervals etc.




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- **Computer implementation:**
 - ◆ Available in R, S--PLUS and SPSS (*not Minitab*)
 - ◆ All packages produce a table of parameter estimates and standard errors for each factor
 - ◆ **R**
 - Construct `Surv(.)` object first then use `coxph()`
 - ◆ **S-PLUS:**
 - `Statistics>Survival>Cox Proportional Hazards...`
 - ◆ **SPSS:**
 - `Analyze>Survival>Cox Regression`



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- **Methotrex data:**
 - ◆ Data on liver survival:
 - Time variable is **FOLLOWUP**
 - Censoring in **STATUS**
 - Various covariates and prognostic factors
 - **TREATMNT** (0=placebo, 1=methotrex)
 - **MAYO** is a key covariate




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```

> library(survival)
Loading required package: splines
> attach(methotrex)
> methotrex[1:4, ]
  TREATMNT STATUS FOLLOWUP   MAYO LUDWIG BILIRUBEN PROTHROM ALBUMIN AGE AMA
1         0      0        28 4.796029      2      15    12.86   4.2  63  1
2         0      1        32 5.883894      2      74    12.00   4.3  61  1
3         0      1        34 4.868391      4      33    11.76   4.7  60  1
4         0      0        37 4.531851      2      16    12.20   3.6  48  1

> meth.sv<-Surv(FOLLOWUP, STATUS)
> meth.ph<-coxph(meth.sv~TREATMNT+MAYO)
> summary(meth.ph)
    
```



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```
> summary(meth.ph)
Call:
coxph(formula = meth.sv ~ TREATMNT + MAYO)
  n= 60
      coef exp(coef) se(coef)      z Pr(>|z|)
TREATMNT1 0.4358  1.5462  0.5646 0.772  0.44
MAYO      0.7543  2.1261  0.1811 4.164 3.12e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

      exp(coef) exp(-coef) lower .95 upper .95
TREATMNT1    1.546    0.6468    0.5113    4.675
MAYO         2.126    0.4703    1.4907    3.032

Rsquare= 0.224 (max possible= 0.826 )
Likelihood ratio test= 15.25 on 2 df, p=0.000487
Wald test              = 19.56 on 2 df, p=5.657e-05
Score (logrank) test = 22.58 on 2 df, p=1.250e-05
```

	coef	exp(coef)	se(coef)	z	p
TREATMNT	0.436	1.55	0.565	0.772	0.440000
MAYO	0.754	2.13	0.181	4.164	0.000031

	exp(coef)	exp(-coef)	lower .95	upper .95
TREATMNT	1.55	0.647	0.511	4.68
MAYO	2.13	0.470	1.491	3.03

Note that this gives estimates & confidence intervals for β and $\exp(\beta)$

S-PLUS output

	coef	exp(coef)	se(coef)	z	p
TREATMNT	0.436	1.55	0.565	0.772	0.440000
MAYO	0.754	2.13	0.181	4.164	0.000031

	exp(coef)	exp(-coef)	lower .95	upper .95
TREATMNT	1.55	0.647	0.511	4.68
MAYO	2.13	0.470	1.491	3.03

SPSS output

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)
TREATMNT	.446	.565	.621	1	.431	1.561
MAYO	.753	.181	17.301	1	.000	2.124

SPSS output

Variables in the Equation


	B	SE	Wald	df	Sig.	Exp(B)
TREATMNT	.446	.565	.621	1	.431	1.561
MAYO	.753	.181	17.301	1	.000	2.124

(Wald statistic is same as chi-squared)

- More on interpretation of coefficients
 - Interactions:
 - If 2 covariates **interact** it means that the effect of one of them **depends** upon the value of the other
 - i.e effect different for different levels
 - e.g. treatment \times stage of cancer interaction
 - treatment only effective for stage 2 not stage 1




- Could be that the two **main effects** have non-significant coefficients but their [2-way] interaction is significant
- Cannot ignore main effects
 - even if main coefficients 'insignificant'
 - ♦ Need to include main effect coefficients as well as interaction term in model interpretation




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- Mathematically express [linear] interactions as a product of the two variables which interact
 - ♦ e.g. A & B 2-level factors coded by x_1 & x_2 taking values 0 & 1
 - ♦ Define interaction as $x_3 = x_1 \times x_2$




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- ♦ So if model is $h(t) = h_0(t) \exp(\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3)$
 - $x_3 = x_1 \times x_2$
- ♦ Then
 - $h(t) = h_0(t)$ for $x_1 = 0, x_2 = 0$
 - $h(t) = h_0(t) \exp(\beta_1)$ for $x_1 = 1, x_2 = 0$
 - $h(t) = h_0(t) \exp(\beta_2)$ for $x_1 = 0, x_2 = 1$
 - $h(t) = h_0(t) \exp(\beta_1 + \beta_2 + \beta_3)$ for $x_1 = 1, x_2 = 1$
 - Similarly if one or both of A & B are continuous



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- Example:-
 - ♦ $x_1 = 0$ or 1 for placebo & treatment
 - ♦ $x_2 = \log_{10}$ (white blood cell count)
 - ♦ $x_3 = x_1 \times x_2 =$ interaction



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- Estimates: =

factor	estimate	st. error
x_1 (treatment)	-1.34	0.72
x_2 (\log_{10} {w.b.c})	+1.65	0.82
$x_3 = x_1 \times x_2$ (interaction)	-1.31	0.41




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- Estimates: =

Factor	estimate	st. error	p-value
x_1 (treatment)	-1.34	0.72	> 0.05
x_2 (\log_{10} {w.b.c})	+1.65	0.82	~ 0.05
$x_3 = x_1 \times x_2$ (interaction)	-1.31	0.41	< 0.05

- ♦ Not justified to say treatment has no effect
 - Treatment-by-wbc interaction **important**



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- On placebo model estimated as
 - ◆ $h(t) = h_0(t)\exp\{1.65 \times \log_{10}(wbc)\}$
 - i.e. survival poorer with higher wbc
- On treatment model estimated as
 - ◆ $h(t) = h_0(t)\exp\{-1.34 + 1.65 \times \log_{10}(wbc) - 1.31 \times \log_{10}(wbc)\}$
 $= h_0(t)\exp\{-1.34 + 0.34 \times \log_{10}(wbc)\}$
 - i.e. effect of treatment is to lessen greatly effect of increased wbc
 - $\log_{10}(wbc)$ has to be above $1.34/0.34 \approx 4$ for increased wbc to severely affect survival of those on active treatment
 - i.e. wbc > 10,000 before treatment is overwhelmed

- **Model checking**
 - ◆ log-log plots
 - (log-minus-log)
 - ◆ e.g. two groups: plot $\log_e[-\log_e\{\hat{S}_j(t)\}]$ vs t for each group

Proportional hazards \Rightarrow parallel curves
 Curves cross \Rightarrow not proportional hazards

- **Log-log plots in R (& S-plus)**
 - Need to fit model separately to levels of factor
 - First change data type to factor
 - Then fit this as a 'strata'
 - Produces separate R 'survival objects'
 - One for each stratum, i.e. each factor level
 - Can then plot separate survival curves

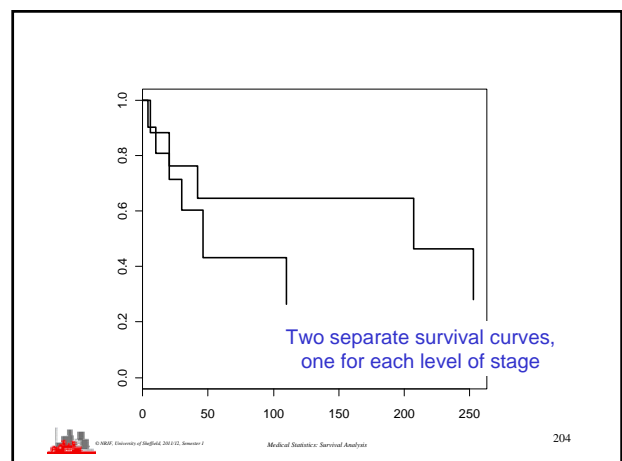
- **Example: lymphoma data**
 - Variables time, censor, stage
 - ◆ FIRST need to 'attach' data set
 - `attach(lymphoma)`
 - ◆ Change data type to factor
 - `stage <- factor(stage)`
 - ◆ Use R function for Cox model, `coxph()`

```

> attach(lymphoma)
> stage <- factor(stage)
> lymph.cox <- coxph(Surv(time, censor) ~ strata(stage))
> lymph.cox
Call: coxph(formula = Surv(time, censor) ~ strata(stage))

Null model
log likelihood = -17.77164
n = 18
> plot(survfit(lymph.cox))
    
```

Note use of `strata()` & use of `survfit()` to obtain object for plotting

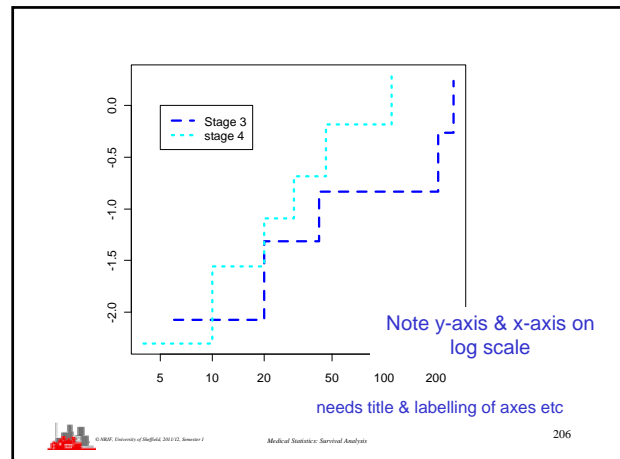


- Now need to plot on different vertical scale:
 - i.e. log-log or 'complementary log log'
 - Use argument `fun="cloglog"` in plot call
 - can also choose line styles with `lty=...`
 - and colours with `col=...`

```

> plot(survfit(lymph.cox), fun="cloglog", lty=2:3, col=4:5)
> legtext<-c("Stage 3", "stage 4")
> legend(5, 0, legtext, lty=2:3, col=4:5, lwd=3)
    
```

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- Note:
 - using a factor as a strata indicator fits separate models to each level so we do not have a coefficient for that factor

```

> lymph.cox2<-coxph(Surv(time,censor)~stage)
> lymph.cox2
Call:
coxph(formula = Surv(time, censor) ~ stage)
      coef exp(coef) se(coef)      z      p
stage 0.29      1.34      0.33 0.877 0.38

Likelihood ratio test=0.79 on 1 df,
p=0.374 n= 18
    
```

Note absence of `strata()`

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- Note: to obtain any survival estimate we will have to average over values of any covariate not declared as a stratum indicator
 - e.g. for Prostatic data to produce a log-log plot for the treatment groups declare `treatment` as a strata factor variable and then estimate survivor curves averaged over age, serum, size and Gleason index
 - For log-log plots of Gleason index declare `treatment` as ordinary factor and `Gleason` as strata.

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Example: Methrex data

```

> library(survival)
Loading required package: splines
> attach(methtrex)
> methtrex[1:3,]
  TREATMNT STATUS FOLLOWUP  MAYO LUDWIG BILIRUBN PROTHROM ALBUMIN AGE AMA
1      0      0      28 4.796029      2      15 12.86      4.2 63  1
2      0      1      32 5.883894      2      74 12.00      4.3 61  1
3      0      1      34 4.868391      4      33 11.76      4.7 60  1
    
```

```

> methsurv<-Surv(FOLLOWUP, STATUS)
    
```

Create survival object for plotting and dependent object in regression

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Example: Methrex data

Consider first treatment factor

```

> meth.treat<-coxph(methsurv~ TREATMNT+ MAYO)
> summary(meth.treat)
Call:
coxph(formula = methsurv ~ TREATMNT + MAYO)
      n= 60
      coef exp(coef) se(coef)      z Pr(>|z|)
TREATMNT1 0.4358      1.5462      0.5646 0.772      0.44
MAYO      0.7543      2.1261      0.1811 4.164 3.12e-05
    
```

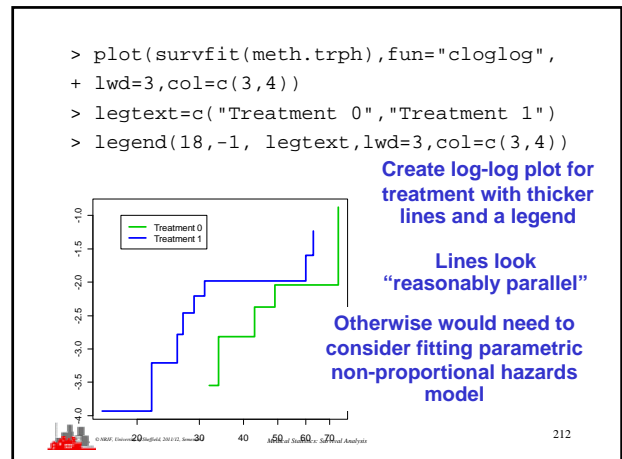
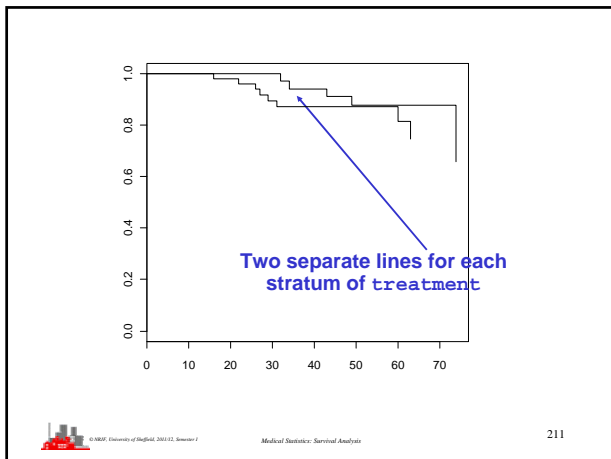
```

> meth.trph<-coxph(methsurv~strata(TREATMNT)+ MAYO)
> plot(survfit(meth.trph))
    
```

Re-fit with `treatment` as a stratum indicator for diagnostic plotting

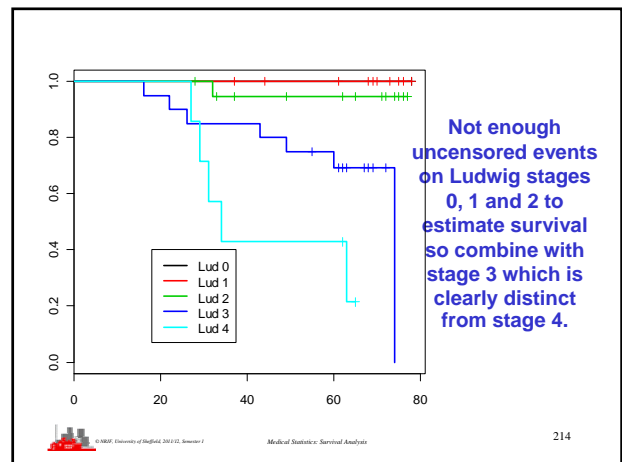
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```

♦ Now consider factor LUDWIG
> summary(LUDWIG)
 0  1  2  3  4
1 12 20 20  7
# small frequencies at some levels
# exploratory K-M plot useful
> ludfit<-survfit(methsurv~LUDWIG)
> plot(ludfit,lwd=2,col=c(1:5))
> legtext<-c("Lud 0","Lud 1","Lud 2",
+ "Lud 3","Lud 4")
> legend(18,0.4, legtext,lwd=2,col=c(1:5))
>
    
```



```

>
> LUD2<- LUDWIG
> levels(LUD2)<- list(A=c(0,1,2,3),B=4)
> summary(LUD2)
  A  B
53  7
> meth2.anal<-coxph(methsurv~LUD2+TREATMNT+MAYO+BILIRUBN)
> summary(meth2.anal)
Call:
coxph(formula = methsurv ~ LUD2 + TREATMNT + MAYO +
      BILIRUBN)

n= 60

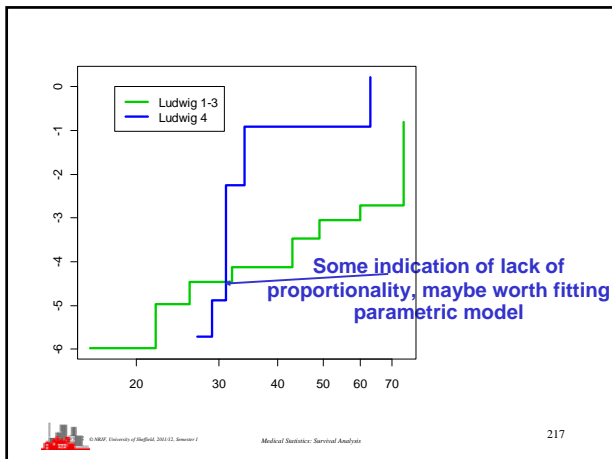
      coef exp(coef) se(coef)      z Pr(>|z|)
LUD2B    1.49837   4.47441  0.73770  2.031 0.042240 *
TREATMNT1 0.89523   2.44789  0.65551  1.366 0.172033
MAYO      0.67999   1.97386  0.29439  2.310 0.020897 *
BILIRUBN  0.05567   1.05725  0.01685  3.304 0.000955 ***
    
```

```

> meth2.ph<-coxph(methsurv~strata(LUD2)+
+ TREATMNT+ MAYO+BILIRUBN)
> plot(survfit(meth2.ph))
> plot(survfit(meth2.ph), fun="cloglog",
+ lwd=3,col=c(3,4))
> legtext=c("Ludwig 1-3","Ludwig 4")
> legend(18,0, legtext,lwd=3,col=c(3,4))
    
```

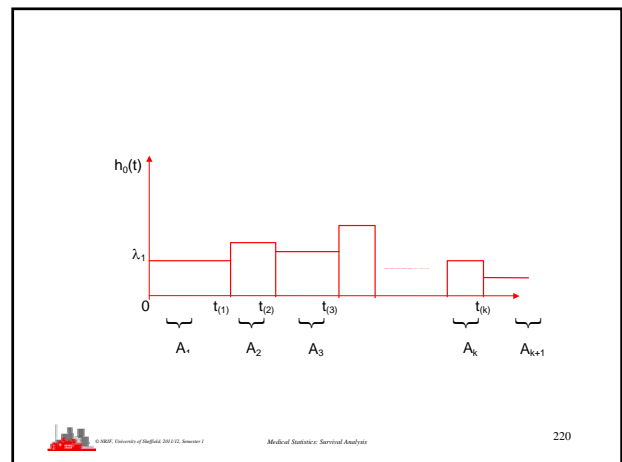
Re-fit with LUD2 as a stratum indicator for diagnostic plotting





- Log-log plots in SPSS:
 - Obtained from menu *Analyze>Survival>Cox Regression*
 - Ensure factor variables are declared as *categorical*
 - Check *log minus log* box under *Plots...* dialogue
 - Ensure factor *separate lines for:* box is completed

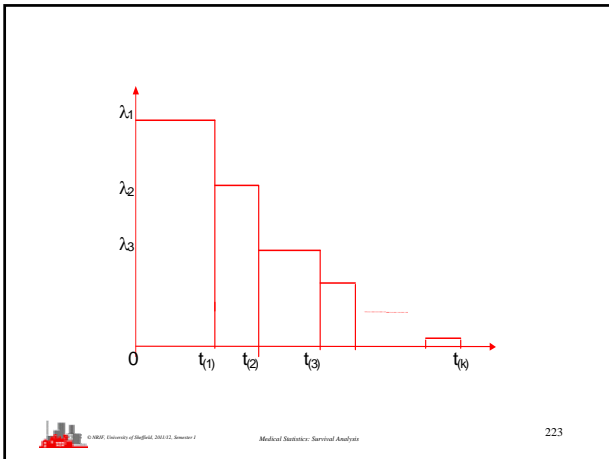
- Estimation of $h(t)$
 - ◆ No information about $h(t)$ in intervals with no failures –
 - $h_0(t)$ is arbitrary (possibly even 0 in interval)
 - ◆ Assume that the hazard constant (at λ_i) between adjacent death times
 - (since no information that it is **not** constant)



- Estimate $\underline{\beta}$ by max. partial likelihood
 - Define $\lambda_j = h_0(t)$ if $t \in A_j = (t_{(j-1)}, t_{(j)})]$
 - Estimate λ_j by MLE, replacing $\underline{\beta}$ by $\hat{\underline{\beta}}$
- $$\Rightarrow \hat{\lambda}_j = \frac{d_j}{\sum_{i \in R(t_{(j)})} e^{\hat{\underline{\beta}}x} (t_{(j)} - t_{(j-1)}) + \sum_{i \in A_j} e^{\hat{\underline{\beta}}x} (t_i - t_{(j-1)})}$$

- pattern in estimates of λ_j may identify \Rightarrow parametric form for $h_0(t)$.
 - ◆ roughly constant \Rightarrow exponential survival
 - ◆ Linear increasing \Rightarrow Weibull shape =2
 - ◆ Exponentially decreasing \Rightarrow Gumbel





- **Proportional Hazards Models**
 - ◆ Only models dependence on covariates
 - ◆ No statements about survival times
 - ◆ Only effect of covariates on hazards
 - ◆ Estimation by maximum partial likelihood
 - Check proportional hazards by log-log plots
 - ◆ Estimation of hazard may suggest parametric model

- Key diagnostic is log-log plots
 - ◆ Other techniques use residuals (see Schoenfeld residuals etc)
 - Try `help(residuals.coxph)` & `help(residuals.survreg)`
- No allowance for individual variability
 - ◆ i.e. no term in σ_i^2 for i^{th} individual
 - ◆ **Frailty models** do allow for this
 - ◆ Some facilities in R



- That was the end of the course (almost)
- What other important topics are there in Survival Analysis?
 - ◆ **Accelerated failure time models**
 - ◆ (Time-dependent covariates)
 - ◆ **Competing risks models**

- ◆ **Accelerated failure time models**
 - Survivor function has the form $S(t;\mathbf{x}) = S_0(t.e^{\beta\mathbf{x}})$
 - Effect of covariates is to 'accelerate time'
 - Weibull models have the **accelerated failure time property**
 - proportional hazards model with the acft property
 - » Others are Gompertz, Extreme Value, Loglogistic
 - name from accelerated-life testing,
 - e.g. to test electronic components raise voltage
 - need to ensure model is appropriate for this situation & not think use of model will accelerate experiment
 - ◆ Needs R library `eha` & function `aftreg(.)`
 - use `surv(.)` first to create survival object



- **Competing risks models**
 - ◆ Subject at risk from several different causes
 - Event caused by 'whichever gets them first'
 - (i.e. risks compete)
 - ◆ Hazards are 'cause-specific' & may depend differently on covariates
 - ◆ Example is death after transplant: causes could be:-
 - Rejection
 - Infection
 - Heart failure
 - etc
 - ◆ Or infection from a virus/bacterium/.....



- Key complication is censored observations are not associated with a specific cause
 - ◆ Death from one cause removes subject from risk set of death from other causes
 - (assuming you can only die once)
 - ◆ Infection from one bug may alter risks for infection from other causes
- **Competing risks models in R**
 - ◆ Many different facilities in different specialist libraries
 - ◆ Library `cmprsk`, use `surv()` first as always



The End

