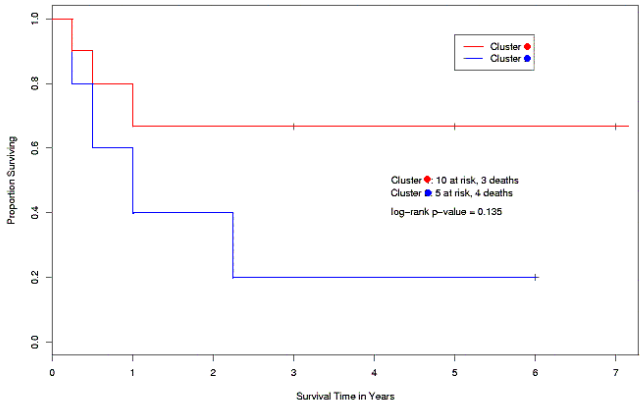
Survival Analysis



http://www.isrec.isb-sib.ch/~darlene/EMBnet/

Modeling review

- Want to capture important features of the *relationship* between a (set of) *variable(s)* and (one or more) *responses*
- Many models are of the form

$$g(Y) = f(\underline{x}) + \text{error}$$

- *Differences* in the form of g, f and distributional assumptions about the error term

Examples of Models

- Linear: $Y = \beta_0 + \beta_1 x + \varepsilon$
- Linear: $Y = \beta_0 + \beta_1 x + \beta_2 x^2 + \varepsilon$
- (Intrinsically) Nonlinear:

$$Y = \alpha x_1^{\beta} x_2^{\gamma} x_3^{\delta} + \varepsilon$$

- Generalized Linear Model (e.g. Binomial):

$$\ln(p/[1-p]) = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

- Proportional Hazards (in Survival Analysis):

$$h(t) = h_0(t) \exp(\beta x)$$

Survival data

- In many medical studies, an outcome of interest is the *time to an event*
- The event may be
  - *adverse* (e.g. death, tumor recurrence)
  - *positive* (e.g. leave from hospital)
  - *neutral* (e.g. use of birth control pills)
- Time to event data is usually referred to as *survival data* – even if the event of interest has nothing to do with 'staying alive'
- In engineering, often called *reliability data*

Censoring

- If all lifetimes were *fully observed*, then we have a *continuous variable*
- We have already looked at some methods for analyzing continuous variables
- For survival data, the event may not have occurred for all study subjects during the follow-up period
- Thus, for some individuals we will not know the exact lifetime, only that it *exceeds some value*
- Such incomplete observations are said to be *censored*

Survival modeling

- Response T is a (nonnegative) *lifetime*
- For most random variables we work with the cumulative distribution function (cdf) *F(t)* (=P(T <= t)) and the density function *f(t)* (=height of the histogram)
- For lifetime (survival) data, it's more usual to work with the *survival function*

$$S(t) = 1 - F(t) = P(T > t)$$

and the *instantaneous failure rate*, or hazard function

$$h(t) = \lim_{\Delta t \to 0} P(t \leq T < t+\Delta t \mid T \geq t)/\Delta t$$

Survival function properties

- The *survival function*

  $$S(t) = 1 - F(t) = P(T > t)$$

  is the probability that the time to event is *later* than some specified time
- Usually assume that $S(0) = 1$ – that is, the event is certain to occur after time 0
- The survival function is *nonincreasing*:

  $S(u) <= S(t)$ if time u > time t
- That is, survival is less probable as time increases
- $S(t) \rightarrow 0$ as $t \rightarrow \infty$ (no 'eternal life')

Relations between functions

- Cumulative hazard function

  $$H(t) = \int_0^t h(s)\, ds$$
- $h(t) = f(t)/S(t)$
- $H(t) = -\log S(t)$

Kaplan-Meier estimator

- In order to answer questions about T, we need to estimate the survival function
- Common to use the *Kaplan-Meier* (also called *product limit*) *estimator*
- 'Down staircase', typically shown graphically
- When there is no censoring, the KM curve is equivalent to the empirical distribution
- Can test for differences between groups with the *log-rank test*

Cox proportional hazards model

- *Baseline hazard* function $h_0(t)$
- Modified *multiplicatively* by covariates
- Hazard function for individual case is

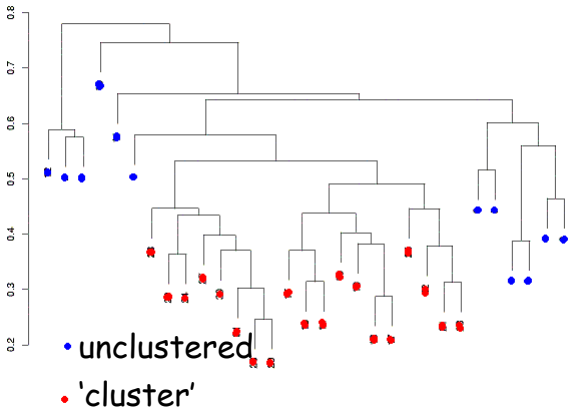
$$h(t) = h_0(t) \exp(\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p)$$

- If nonproportionality:
  - 1. Does it matter
  - 2. Is it real

Example: Survival analysis with gene expression data

- Bittner *et al.* dataset:
  - 15 of the 31 melanomas had associated *survival times*
  - 3613 'strongly detected' genes

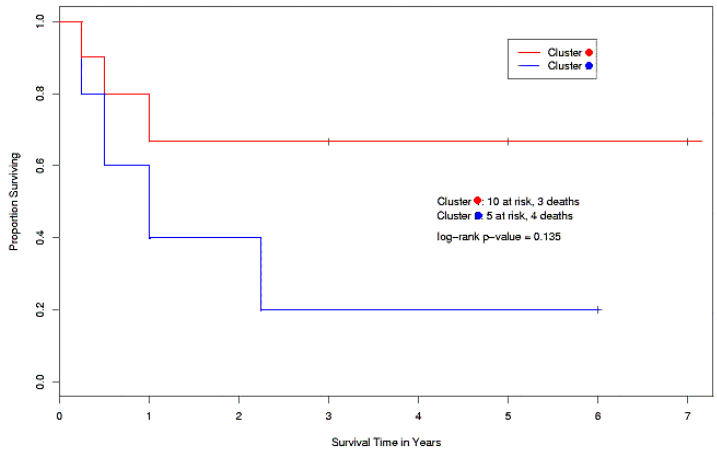
Average linkage hierarchical clustering



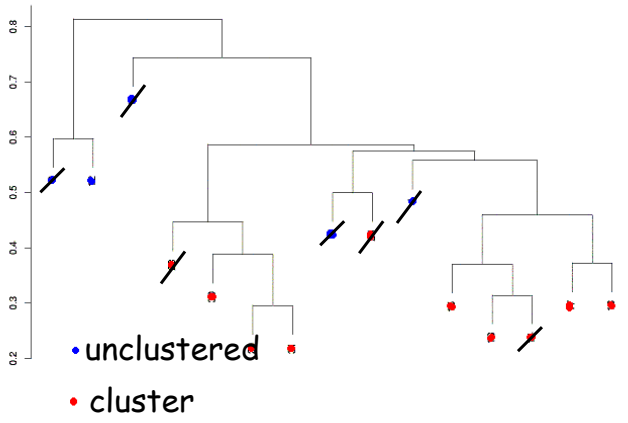
Survival analysis: Bittner et al.

- Bittner et al. also looked at differences in *survival* between the two groups (the 'cluster' and the 'unclustered' samples)
- The 'cluster' seemed associated with longer survival

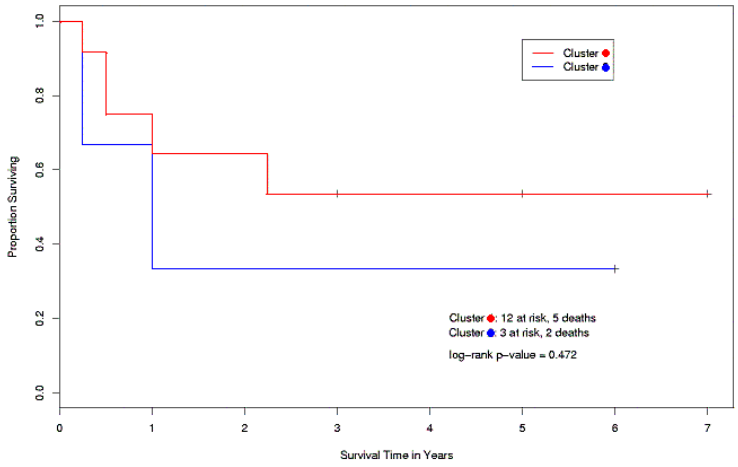
Kaplan-Meier survival curves



Average linkage hierarchical clustering, survival samples only



Kaplan-Meier survival curves, new grouping



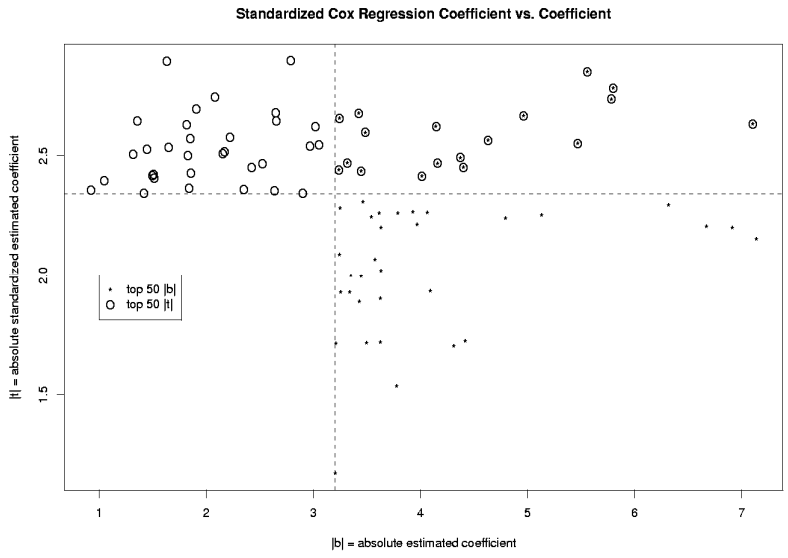
Identification of genes associated with survival

- For each gene *j*, *j* = 1, …, 3613, model the *instantaneous failure rate*, or hazard function, *h(t)* with the Cox proportional hazards model:

$$h(t) = h_0(t)\exp(\beta_j x_{ij})$$

and look for genes with *both* :

- large effect size $\hat{\beta}_j$
- large *standardized* effect size $\hat{\beta}_j / \hat{SE}(\beta_j)$



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Advantages of modeling

- Can address questions of interest *directly*
  - Contrast with the indirect approach: clustering, followed by tests of association between cluster group and variables of interest
- Great deal of *existing machinery*
- *Quantitatively* assess strength of evidence

Survival analysis in R

- R package **survival**
- A survival object is made with the function **Surv()**
- What you have to tell **Surv**
  - **time** : observed survival time
  - **event** : indicator saying whether the event occurred (**event=TRUE**) or is censored (**event=FALSE**) Analyze with Kaplan-Meier curve: **survfit**, log-rank test: **survdiff**
- Cox proportional hazards model: **coxph**