STK4080/9080 SURVIVAL AND EVENT HISTORY ANALYSIS

Slides 15: Unobserved heterogeneity

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Heterogeneity in survival analysis

In Chapter 3 of ABG we assumed that individuals in a population *share the same survival distribution* (hazard etc.) Or, we considered two or more such populations and compared their hazard functions.

In Chapter 4 we introduced **survival regression**, where differences between individuals in a populations were modeled in terms of hazard functions that are functions of **observable** covariates.

There may, however, be other differences between individuals which we *do not measure* or which we *may not know* about:

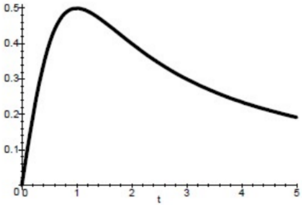
- Such unobserved differences may be due to:
  - Environment
  - Life style
  - Genes
- *The unobserved differences are often disregarded when analyzing survival data.*
- **As explained in the frailty theory, we should take these unobserved differences into account in our analyses.**

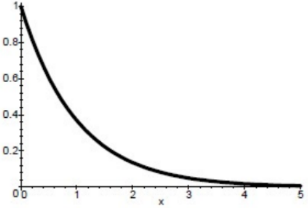
Population hazard and individual hazard

- We will distinguish between the *population hazard* rate and the *individual* hazard rates.
- The population hazard rate is influenced by selection: those with highest risk experience the event early.
- The shape of the population hazard may be entirely different from that of the individual hazards.
- Hence the population hazard can not generally be interpreted as giving information on individual development in risk.

Typical shapes of population hazard rates seen in data

Hazard rates that first increase and later decrease are common in practice, and may be due to a frailty effect.





- (Left) Mortality rate of cancer patients, measured from the time of diagnosis, typically first increases, then reaches a maximum, and then starts to decline. A likely reason is *heterogeneity from the outset as regards the prospect of recovery.*
- (Right) Mortality of patients with myocardial infarction starts to decline shortly after the infarction has taken place. Again, one would expect that survivors have had a less serious attack and so better chances from the beginning.

A simple example

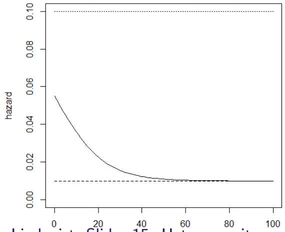
Suppose we have a batch of electronic components where

- Half have a lifetime which is exponential with expected value 100
- Half have a lifetime which is exponential with expected value 10

You draw randomly a number of components from the batch and estimate the hazard function for this sample. What do you see?

You are estimating the hazard function for a randomly drawn component:

$$\alpha(t) = \frac{f(t)}{S(t)} = \frac{(1/2)(1/100)\exp(-t/100) + (1/2)(1/10)\exp(-t/10)}{(1/2)\exp(-t/100) + (1/2)\exp(-t/10)}$$



More generally,...

Assume a population is composed of two groups, a "low risk group" and a "high risk group".

Let the proportions in the two groups be p_1 and $p_2 = 1 - p_1$.

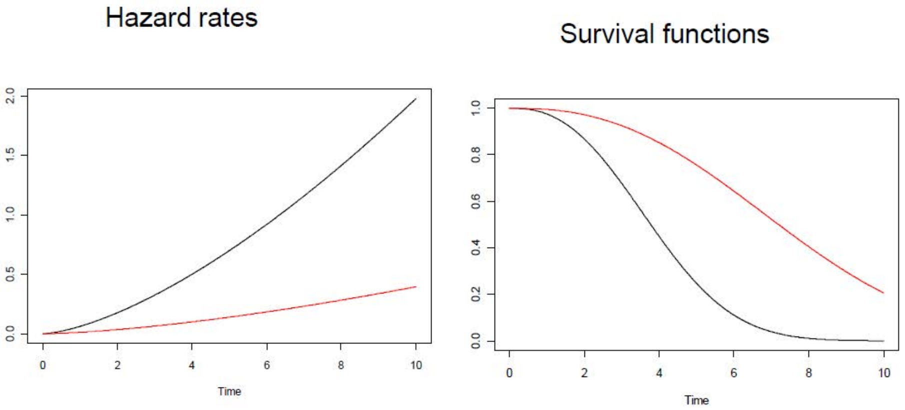
The low risk group has hazard $\alpha_1(t)$ and survival function

$$S_1(t) = \exp\left\{-\int_0^t \alpha_1(u)du\right\}$$

The high risk group has hazard $\alpha_2(t)$ and survival function

$$S_2(t) = \exp\left\{-\int_0^t \alpha_2(u)du\right\}$$

Illustration



Red: low risk Black: high risk

Population hazard and survival

Population survival function

$$S(t) = p_1 S_1(t) + p_2 S_2(t)$$

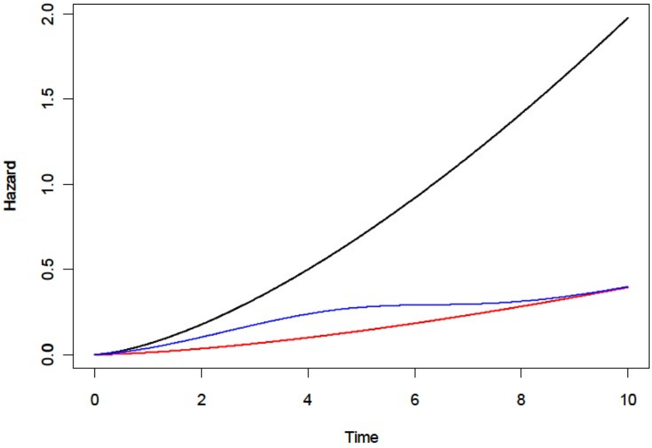
Population hazard rate

$$\begin{aligned}
\mu(t) &= -\frac{S'(t)}{S(t)} = -\frac{p_1 S_1'(t) + p_2 S_2'(t)}{p_1 S_1(t) + p_2 S_2(t)} \\
&= \frac{p_1 S_1(t)}{p_1 S_1(t) + p_2 S_2(t)} \left(-\frac{S_1'(t)}{S_1(t)} \right) \\
&+ \frac{p_2 S_2(t)}{p_1 S_1(t) + p_2 S_2(t)} \left(-\frac{S_2'(t)}{S_2(t)} \right) \\
&= w_1(t)\alpha_1(t) + (1 - w_1(t))\alpha_2(t)
\end{aligned}$$

where

$$w_1(t) = \frac{p_1 S_1(t)}{p_1 S_1(t) + p_2 S_2(t)}$$

Illustration



Red: low risk

Black: high risk

Blue: population

The proportional frailty model

Instead of assuming that the population has just two kinds of individuals (*high risk* and *low risk*, e.g.), we now assume that the heterogeneity between individuals may be described by a **frailty variable** Z.

Z is a non-negative random variable. Each individual has its "own" Z, where large values of Z corresponding to "frail" individuals.

The assumption is that an individual with frailty Z has a hazard function

$$\alpha(t|Z) = Z \cdot \alpha(t),$$

where $\alpha(t)$ is a baseline hazard (corresponding to $Z = 1$).

It is commonly assumed that $E(Z) = 1$.

Note that the frailty Z is not observable.

Gamma distributed frailties

The most common choice of distribution for the frailty Z is the gamma distribution with density

$$f(z) = \frac{\nu^\eta}{\Gamma(\eta)} z^{\eta-1} e^{-\nu z}; \quad z > 0$$

The expected value is η/ν and the variance η/ν^2.

Assuming $E(Z) = 1$, we have $\eta = \nu$, and the variance then becomes

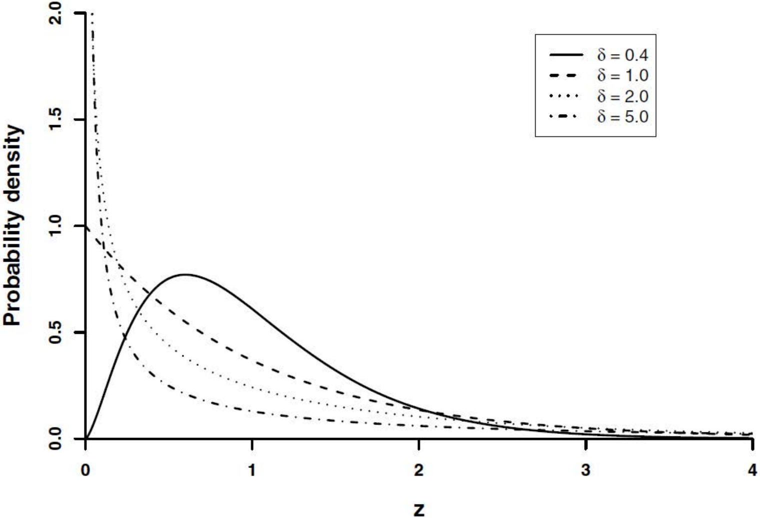
$$Var(Z) = \frac{\eta}{\nu^2} = \frac{1}{\nu} \equiv \delta$$

δ is hence a convenient parameter to be used for a gamma frailty distribution (and is then the only parameter). The density of Z becomes

$$f(z) = \frac{1}{\delta^{1/\delta}\Gamma(1/\delta)} z^{(1/\delta)-1} e^{-z/\delta}$$

Gamma densities with expectation 1 and variance δ

$$f(z) = \frac{1}{\delta^{1/\delta}\Gamma(1/\delta)} z^{(1/\delta)-1} e^{-z/\delta}$$



Laplace transform

The Laplace transform is a convenient tool to study the proportional frailty model.

For a positive random variable Z the Laplace transform is given by

$$\mathcal{L}(c) = E(e^{-cZ})$$

The Laplace transform is closely related to the moment generating function

$$\mathcal{M}(s) = E(e^{sZ})$$

Gamma distribution

For the gamma distribution with density

$$f(z) = \frac{\nu^\eta}{\Gamma(\eta)} z^{\eta-1} e^{-\nu z}; \quad z > 0$$

it is well known that the moment-generating function is

$$\mathcal{M}(s) = \left(\frac{1}{1 - s/\nu} \right)^\eta$$

so the Laplace transform becomes

$$\mathcal{L}(c) = \mathcal{M}(-c) = \left(\frac{1}{1 + c/\nu} \right)^\eta$$

In particular for the gamma distribution with mean 1 (i.e. $\eta = \nu$) and variance $\delta = 1/\nu$ the Laplace transform takes the form

$$\mathcal{L}(c) = (1 + c/\nu)^{-\nu} = (1 + \delta c)^{-1/\delta}$$

Population survival function

Consider a population where the heterogeneity is described by the proportional frailty model, i.e., an individual with frailty Z has the hazard

$$\alpha(t|Z) = Z\alpha(t)$$

and hence the survival function

$$S(t|Z) = e^{-\int_0^t \alpha(u|Z)du} = e^{-Z\int_0^t \alpha(u)du} = e^{-ZA(t)}$$

where $A(t) = \int_0^t \alpha(u)du$.

Let now T be the survival time of a randomly selected individual from the population. Then

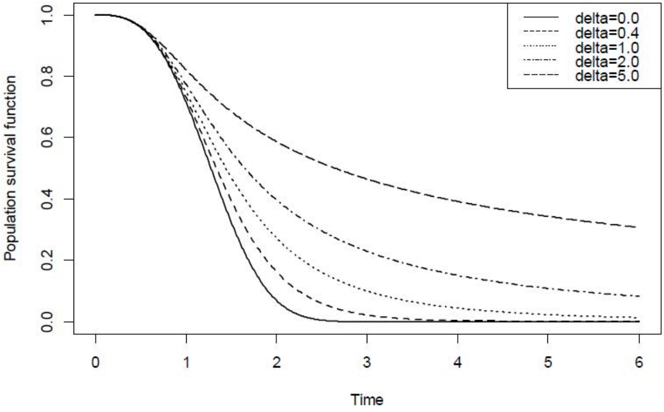
$$\begin{aligned} S(t) &= P(T > t) = E(P(T > t|Z)) \\ &= E(e^{-ZA(t)}) = \mathcal{L}(A(t)) \end{aligned}$$

Gamma distributed frailties

If the frailty Z is gamma distributed with mean 1 and variance δ, the population survival function becomes

$$S(t) = \mathcal{L}(A(t)) = \{1 + \delta A(t)\}^{-1/\delta}$$

Example: Let $\alpha(t) = t^2$, so $A(t) = (1/3)t^3$:



Population hazard

The population hazard becomes

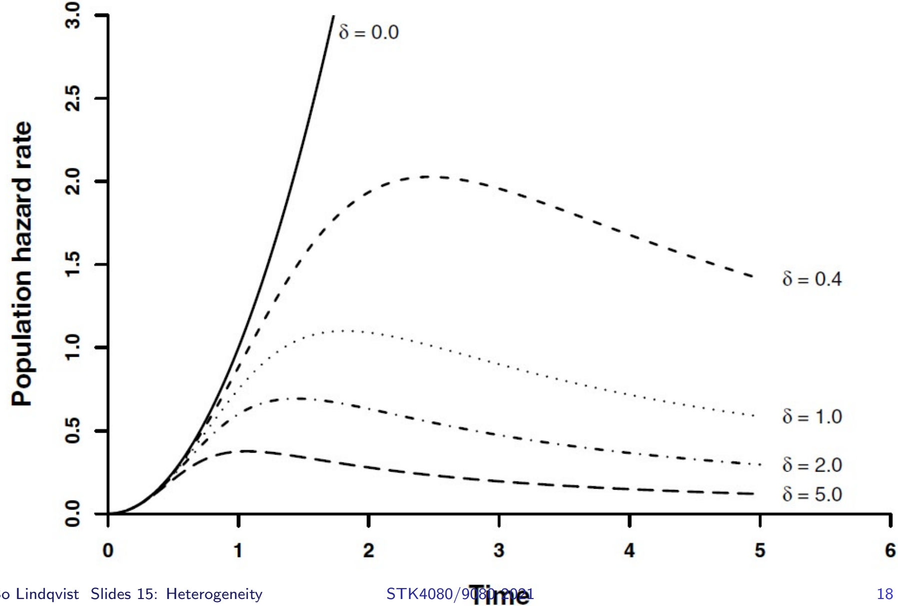
$$\mu(t) = \frac{-S'(t)}{S(t)} = \frac{-(d/dt)\mathcal{L}(A(t))}{\mathcal{L}(A(t))} = \alpha(t)\frac{-\mathcal{L}'(A(t))}{\mathcal{L}(A(t))}$$

If frailty Z is gamma distributed with mean 1 and variance δ, then $\mathcal{L}(c) = (1+\delta c)^{-1/\delta}$, so $\mathcal{L}'(c) = -(1+\delta c)^{(-1/\delta)-1}$. Hence we get

$$\mu(t) = \alpha(t)\frac{(1+\delta A(t))^{-\frac{1}{\delta}-1}}{(1+\delta A(t))^{-\frac{1}{\delta}}} = \frac{\alpha(t)}{1+\delta A(t)}$$

Note: When $\delta = 0$ there is no frailty and $\mu(t) = \alpha(t)$. As δ increases, the denominator becomes larger, and it also increases with time, yielding the typical frailty shape of a hazard function that is "dragged down".

Population hazard with gamma distributed frailties with $\alpha(t) = t^2$



Estimating frailty

- For survival data where only a single event is available for each individual, the frailty effect is not identifiable unless we assume a specific form of the individual baseline hazard rate $\alpha(t)$.
- Frailty models for survival data may be speculative, but they are useful for understanding why the population hazard may have different shapes.
- Estimation of frailty is more relevant for **clustered survival data** and **recurrent event data** (repeated events). (See Slides 16).