Frailty

Frailty Models

A *frailty* model is one in which the survival distribution for the ith individual depends on a random variable U_i. We denote the *individual* survivor, hazard and integrated hazard functions by F_i, h_i and H_i respectively. The corresponding *population* functions are $\bar{F}$, $\bar{h}$ and $\bar{H}$. F_i and $\bar{F}$ are related by

$$\bar{F} = \mathcal{E} F_i$$

where the expectation is taken over the U_i.

Proportional Frailty

A common formulation is the *proportional* frailty model. The individual hazard function has form

$$h_i(t) = U_i h_0(t)$$

where the U_i are identically independently distributed non-negative random variables with unit mean. The common density function is denoted g.

The individual survivor functions are given by

$$F_i(t) = \mathrm{e}^{-U_i H_0(t)}$$

and the population survivor function by

$$\bar{F}(t) = \int_0^\infty g(u) \mathrm{e}^{-u H_0(t)} \,\mathrm{d}u$$

or

$$\bar{F}(t) = \tilde{g}(H_0(t))$$

where $\tilde{g}$ is the Laplace transform of g (see 'Notes on the Laplace Transform' below).

Example: Uniform Frailty Distribution

Suppose the U_i to be uniformly distributed on $[\frac{1}{2}, \frac{3}{2}]$ and the individual survival distributions to be exponential, that is: $h_0(t) = \theta$. The frailty density g is therefore $\mathcal{I}(u \in [\frac{1}{2}, \frac{3}{2}])$ with Laplace transform

$$\tilde{g}(\zeta) = \frac{1}{\zeta} \left[\mathrm{e}^{-\zeta/2} - \mathrm{e}^{-3\zeta/2} \right].$$

The population survivor distribution is given by

$$\bar{F}(t) = \frac{1}{\theta t} \left[\mathrm{e}^{-\theta t/2} - \mathrm{e}^{-3\theta t/2} \right],$$

the integrated hazard by

$$\bar{H}(t) = -\log\left(\frac{1}{\theta t}\left[\mathrm{e}^{-\theta t/2} - \mathrm{e}^{-3\theta t/2}\right]\right)$$

and the hazard by

$$\bar{h}(t) = \frac{1}{t} + \frac{\frac{\theta}{2}\left[\mathrm{e}^{-\theta t/2} - \mathrm{e}^{-3\theta t/2}\right]}{\mathrm{e}^{-\theta t/2} - \mathrm{e}^{-3\theta t/2}}.$$

Note that

$$\lim_{t\downarrow 0}\bar{h}(t) = \theta \qquad \text{and} \qquad \lim_{t\uparrow\infty}\bar{h}(t) = \theta/2.$$

Gamma Distributions with Unit Mean

The gamma distributions with unit mean form a useful family of frailty distributions (see 'Notes on the Gamma distribution' below).

If we define ψ as the reciprocal of the variance of the distribution the Laplace transform of the gamma frailty density is given by:

$$\tilde{g}(\zeta) = \left(\frac{1}{1+\zeta/\psi}\right)^{\psi}.$$

The population survivor function is given for general H_0 by

$$\bar{F}(t) = \left(\frac{1}{1+H_0(t)/\psi}\right)^{\psi}$$

and the population hazard function by

$$\bar{h}(t) = \frac{h_0(t)}{1+H_0(t)/\psi}$$

Note that $\bar{h}(0) = h_0(0)$ and that $\bar{h}(t)/h_0(t)$ is a decreasing function of t.

Lack of Identifiability of g and H_0

It is impossible to determine g and H_0 from $\bar{F}$ alone. For example, if

$$\bar{F}(t) = \frac{1}{1+t}$$

then two of the infinite possibilities for g and H_0 are:

$$(1) \qquad g(t) = \delta(t-1) \qquad \text{and} \qquad H_0(t) = \log(1+t)$$

and

$$(2) \qquad g(t) = \mathrm{e}^{-t} \qquad \text{and} \qquad H_0(t) = t.$$

Attenuation of Hazard Multiplier

Suppose there are two treatment groups labelled by $z \in \{0,1\}$. The individual hazard function of the ith individual in the zth group is given by

$$h_i^{(z)} = U_i^{(z)} \mathrm{e}^{\beta z} h_0(t).$$

Note that at an individual level the hazard functions are exactly proportional.

If the $U_i^{(z)}$ are all identically independent gamma(ψ, ψ) variables then, from the above, the population hazard in the zth group is given by

$$\bar{h}^{(z)}(t) = \frac{\mathrm{e}^{\beta z} h_0(t)}{1 + \mathrm{e}^{\beta z} H_0(t)/\psi}$$

and the population relative risk ratio $r(t) := \bar{h}^{(1)}(t)/\bar{h}^{(0)}(t)$ is given by

$$r(t) = \mathrm{e}^{\beta} \frac{1 + H_0(t)/\psi}{1 + \mathrm{e}^{\beta} H_0(t)/\psi}.$$

The population hazards are not proportional even though the individual hazard functions are. Note that the population hazards start off in the same ratio as the individual hazards ($r(0) = \mathrm{e}^{\beta}$) but the groups get closer together with time ($lim_{t\uparrow\infty} r(t) = 1$). It is dangerous, therefore, to leave out explanatory variables in a proportional hazards model.

Notes on the Laplace Transform

The Laplace transform $\tilde{g}$ of g is defined by

$$\tilde{g}(\zeta) := \int_0^\infty g(u) \mathrm{e}^{-u\zeta} \,\mathrm{d}u$$

whenever the integral exists. If g is a probability density function then the integral always exists and $\tilde{g}(0) = 1$. If the distribution has mean μ and variance σ^2 then $\tilde{g}'(0) = -\mu$ and $\tilde{g}''(0) = \mu^2 + \sigma^2$.

Notes on the Gamma distribution

A random variable distributed as gamma(p, λ) has density

$$g(u) = \frac{\lambda^p u^{p-1}}{(p-1)!} \mathrm{e}^{-\lambda u}$$

with mean p/λ and variance p/λ^2.

The Laplace transform of g is given by

$$\tilde{g}(\zeta) = \left(\frac{\lambda}{\lambda + \zeta} \right)^p.$$

A variable with distribution gamma(ψ, ψ) has unit mean and variance $1/\psi$.