NON-PARAMETRIC MODELS FOR META-ANALYSIS OF SURVIVAL DATA

Hans van Houwelingen, Marta Fiocco, Hein Putter

Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, NL

We consider the situation where a number of studies, n say, have compared treatments A and B on a survival outcome. The basic information is a pair of Kaplan-Meier curves for each study, together with numbers at risk or estimated standard errors. We transform that into a discrete counting process indicating how many patients are at risk, how many die and how many are censored in consecutive intervals for each treatment arm.
We model the potential heterogeneity between studies and the correlation within studies by means of frailty models for the hazards, that is

$$\lambda_{Ai}(t) = \lambda_{A0}(t) Z_{Ai}(t) \text{ and } \lambda_{Bi}(t) = \lambda_{B0}(t) Z_{Bi}(t) \text{ for } i = 1,..,n$$

The "frailties" are allowed to vary over time. They are standardized by requiring $E[Z_{Ai}(t)] \equiv 1,\ E[Z_{Bi}(t)] \equiv 1$. Moreover, the frailty components $(Z_{Ai}(t), Z_{Bi}(t))$ of each study can be dependent.
A very flexible model is the log-normal where $(\ln(Z_{Ai}(t)), \ln(Z_{Bi}(\mathrm{t}))$ are correlated Wiener processes. However, this model is hard to fit and hard to interpret.
We will present a new Gamma-process for $(Z_{Ai}(t), Z_{Bi}(t))$ with the following properties

1. $\mathrm{var}(Z_{Ai}(t)) \equiv \xi_A,\ \mathrm{var}(Z_{Bi}(t)) \equiv \xi_B$
2. $\mathrm{corr}(Z_{Ai}(t), Z_{Bi}(t)) = \rho_{AB}$
3. $\mathrm{corr}(Z_{Ai}(t), Z_{Ai}(s)) = \rho_A^{|s-t|},\ \mathrm{corr}(Z_{Bi}(t), Z_{Bi}(s)) = \rho_B^{|s-t|}$

This process can be seen as an extension of the well-known correlated Gamma-frailty model for paired data.
We will show how the model is constructed and how it can be fitted by two-stage composite likelihood. We will also show some applications to existing data.