A Bayesian, Generalized Frailty Model for Comet Assays

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Abstract

This paper proposes a flexible modeling approach for so-called comet assay data regularly encountered in pre-clinical research. While such data consist of non-Gaussian outcomes in a multi-level hierarchical structure, traditional analyses typically completely or partly ignore this hierarchical nature by summarizing measurements within a cluster. Non-Gaussian outcomes are often modeled using exponential family models. This is true not only for binary and count data, but also for, e.g., time-to-event outcomes. Two important reasons for extending this family are: (1) the possible occurrence of overdispersion, meaning that the variability in the data may not be adequately described by the models which often exhibit a prescribed mean-variance link, and (2) the accommodation of a hierarchical structure in the data, owing to clustering in the data. The first issue is dealt with through so-called overdispersion models. Clustering is often accommodated through the inclusion of random subject-specific effects. Though not always, one conventionally assumes such random effects to be normally distributed. In the case of time-to-event data, one encounters, for example, the gamma frailty model (Duchateau and Janssen 2007). While both of these issues may occur simultaneously, models combining both are uncommon. Molenberghs *et al* (2010) proposed a broad class of generalized linear models accommodating overdispersion and clustering through two separate sets of random effects. Here, we use this method to model data from a comet assay with a three-level hierarchical structure. Whereas a conjugate gamma random effect is used for the overdispersion random effect, both gamma and Normal random effects are considered for the hierarchical random effect. Apart from model formulation, we place emphasis on Bayesian estimation. Our proposed method has upper hand over the traditional analysis in that it: (1) uses the appropriate distribution stipulated in the literature; (2) deals with the complete hierarchical nature; and (3) uses all information instead of summary measures. The fit of the model to the comet assay is compared against the background of more conventional model fits. Results indicate the toxicity of 1,2-Dimethylhydrazine dihydrochloride at different dose levels (low, medium, and high).

Some Keywords: Frailty; Hierarchical model; Random effect; Weibull model.