A flexible class of generalized joint frailty models for the analysis of survival endpoints

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Abstract: This communication addresses shared frailty models for correlated failure times, as well as joint frailty models for the simultaneous analysis of recurrent events (e.g., hospital readmissions) and a major terminal event (typically, death). As extensions of the Cox model, these joint models usually assume a frailty proportional hazards model for each of the recurrent and terminal event processes (Liu *et al.*, 2004; Rondeau *et al.*, 2007). To overcome this assumption, our proposal is to replace these proportional hazards models with generalized survival models (Liu *et al.*, 2017, 2018), for which the survival function is modeled as a linear predictor through a link function. Depending on the link function considered, these can be reduced to proportional hazards, proportional odds, additive hazards or probit models. We first consider a fully parametric framework for the time and covariate effects. For proportional and additive hazards models, our approach also allows the use of smooth functions for baseline hazard functions and time-varying coefficients. The dependence between recurrent and terminal event processes is modeled by conditioning on a shared frailty acting differently on the two processes. Parameter estimates are provided using the maximum (penalized) likelihood method, implemented in the R package `frailtypack` (function `GenfrailtyPenal`). We perform simulation studies to assess the method, which is also illustrated on real datasets.

Key words: Joint Frailty Models; Generalized Survival Models; Recurrent Events; Terminal Event

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