JOINT MODELING OF TWO LONGITUDINAL OUTCOMES AND COMPETING RISK DATA – DYNAMIC EVENT PREDICTIONS

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Abstract

When multiple longitudinal outcomes are collected with survival outcomes it may be of interest to analyze them together. Joint models have recently received a lot of attention due to the fact that they cover a wide range of clinical applications and have promising results. Motivated by a study on patients who received a human tissue valve in the aortic position and were followed echocardiographically, we propose a joint model consisting of two longitudinal outcomes and time-to events. Particularly, the joint model consists of three submodels: a linear mixed-effects model for the longitudinal outcome, a continuation ratio model for the ordinal longitudinal outcome, and cause-specific hazard models for the competing risk failure time data. In the linear mixed-effects submodel we include time as non-linear (using B-splines) for both the fixed and random effects in order to capture the real evolution of the continuous outcome. In the ordinal longitudinal submodel we include linear time in the fixed part and an intercept in the random part. Moreover, both models are corrected for age and gender. For the proportional hazard models, a piecewise constant baseline hazard function is assumed and this model is corrected for age. A time-independent parameterization is assumed for the connection between the longitudinal and survival part, in which the event times depend on the subject-specific level of the longitudinal profiles. For the estimation of the joint model's parameters, we adopt a Bayesian formulation for the proposed model, and derive posterior inferences using a Markov chain Monte Carlo (MCMC) algorithm.

One of the primary questions in this study is to utilize the available data of each patient to provide predicted probabilities for either the two events (re-operation or death). Based on the fitted joint model we derive estimates of cumulative incidence functions that can be dynamically updated as extra longitudinal information is recorded for a patient. Estimation of these probabilities is based on a Monte Carlo scheme suitably designed to propagate uncertainty and produce valid confidence intervals.