A multinomial generalized linear mixed model for clustered competing risks data

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Abstract

Clustered competing risks data are a complex failure time data scheme. Its main characteristics are the cluster structure, which implies a latent within-cluster dependence between its elements, and its multiple variables competing to be the one responsible for the occurrence of an event, the failure. To handle this kind of data, we propose a full likelihood approach, based on a generalized linear mixed model instead a usual complex frailty model. We model the competing causes in the probability scale, in terms of the cumulative incidence function (CIF). A multinomial distribution is assumed for the competing causes and censorship, conditioned on the latent effects. The latent effects are accommodated via a multivariate Gaussian distribution. The CIF is specified as the product of an instantaneous risk level function with a failure time trajectory level function. The estimation procedure is performed through the R package TMB (Template Model Builder), an `C++` based framework with efficient Laplace approximation and automatic differentiation routines. A large simulation study is performed, based on different latent structure formulations. The model presents to be of difficult estimation, with our results converging to a latent structure where the risk and failure time trajectory levels are correlated.

Keywords: Clustered competing risks; Within-cluster dependence; Multinomial generalized linear mixed model (GLMM); TMB: Template Model Builder; Laplace approximation; Automatic differentiation (AD).

1 Introduction

Failure time data is the branch of Statistics responsible to handle random variables describing the time until the occurrence of an event, a failure (Kalbfleisch and Prentice; 2002; Hougaard; 2000). The time until a failure is called survival experience, the modeling object. To accommodate the number of possible causes for a failure and the form how they relate, different failure time data layouts were proposed and are shown in Figure 1. The first two are special cases of the last, a multistate process. The special cases are characterized by the presence of only absorbent states, besides the initial state 0. A multistate process is characterized by the presence of at least one intermediate state. In this

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work, our focus is on the competing risks process, more specifically, its clustered version i.e., with groups of elements sharing some non-observed latent dependence structure.

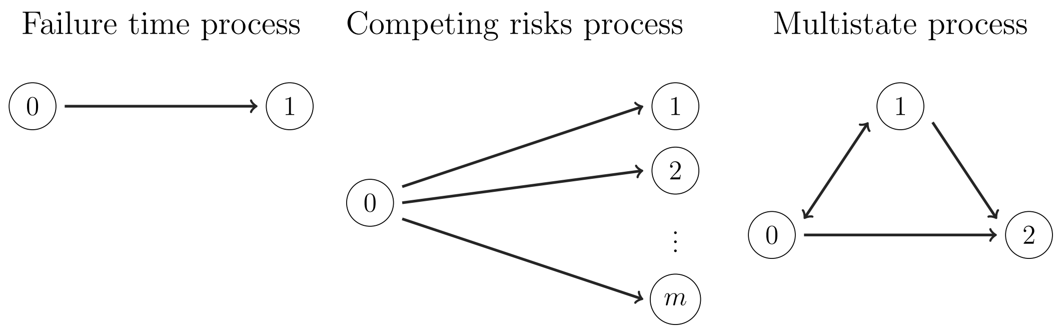

Figure 1: Illustration of failure time data layouts.

In the analysis of failure time data, a survival experiences is usually modeled in the hazard (failure rate) scale, and when the latent within-cluster dependence is accommodated we have a frailty model (Clayton; 1978; Valpel et al.; 1979; Liang et al.; 1995; Petersen; 1998). The use of frailty models implies complicated likelihood functions and its inference is done via elaborated and slow EM algorithms (Nielsen et al.; 1992; Klein; 1992) or inefficient MCMC schemes (Hougaard; 2000). With multiple survival experiences, the general idea is the same but with even more elaborated likelihoods (Prentice et al.; 1978; Therneau and Grambsch; 2000) or via mixture models (Larson and Dinse; 1985; Kuk; 1992).

The inference is attached to the modeling scale i.e., in the usual case the interpretations are in terms of hazard rates. A less usual scale but with a more appealing interpretation, is to model the survival experiences in the probability scale. For competing risks data, the work on the probability scale is done by means of the cumulative incidence function (CIF) (Andersen et al.; 2012), with the main modeling approach being the subdistribution (Fine and Gray; 1999). For clustered competing risks data there are some available options but without any predominance. The differences are basically in terms of likelihood specification, with its majority being designed for bivariate CIFs, where increasing the CIF's dimension is a limitation. Some of the approaches are

- Nonparametric approaches (Cheng et al.; 2007, 2009);
- Linear transformation models (Fine; 1999; Gerds et al.; 2012);
- Semiparametric approaches based on
  - Composite likelihoods (Shih and Albert; 2009; Cederkvist et al.; 2019);
  - Estimating equations (Scheike and Sun; 2012; Cheng and Fine; 2012);
  - Copulas (Scheike et al.; 2010);
  - Mixtures (Naskar et al.; 2005; Shi et al.; 2013).

Besides the interpretation, by modeling the CIF is easier to specify more elaborated within-cluster dependence structures. In this work, we follow Cederkvist et al. (2019) specification based on a decomposition in instantaneous risk and failure time trajectory, with both being cluster-specifics and possible correlated. As a modeling framework, we use a multinomial generalized linear mixed model specification. The class of generalized linear models (GLMs) (Nelder and Wedderburn; 1972) is probably the most popular statistical modelling framework. Despite its flexibility, the GLMs are not suitable for dependent data. For the analysis of such data, Laird and Ware (1982) proposed the random effects regression models for longitudinal/repeated-measures data analysis. Breslow and Clayton (1993) presented the generalized linear mixed models (GLMMs) for the analysis of non-Gaussian outcomes.

The main goal of this study is to propose the . In this paper, we will investigate the as an alternative to . R (R Core Team; 2021) package `TMB` (Kristensen et al.; 2016).

The main contributions of this article are: (i) introducing the unit gamma distribution into the GLMMs framework; (ii) performing a extensive simulation study to check the properties of the the maximum likelihood estimator to deal with longitudinal continuous bounded outcomes; (iii) applying the proposed model in two data sets from different fields of application; (iv) providing R code and `C++` implementation for the unit gamma mixed models.

The work are organized as follows. Section 2, Section 3, Section 4. Finally, the main contributions of the article are discussed in Section 5.

2 Model

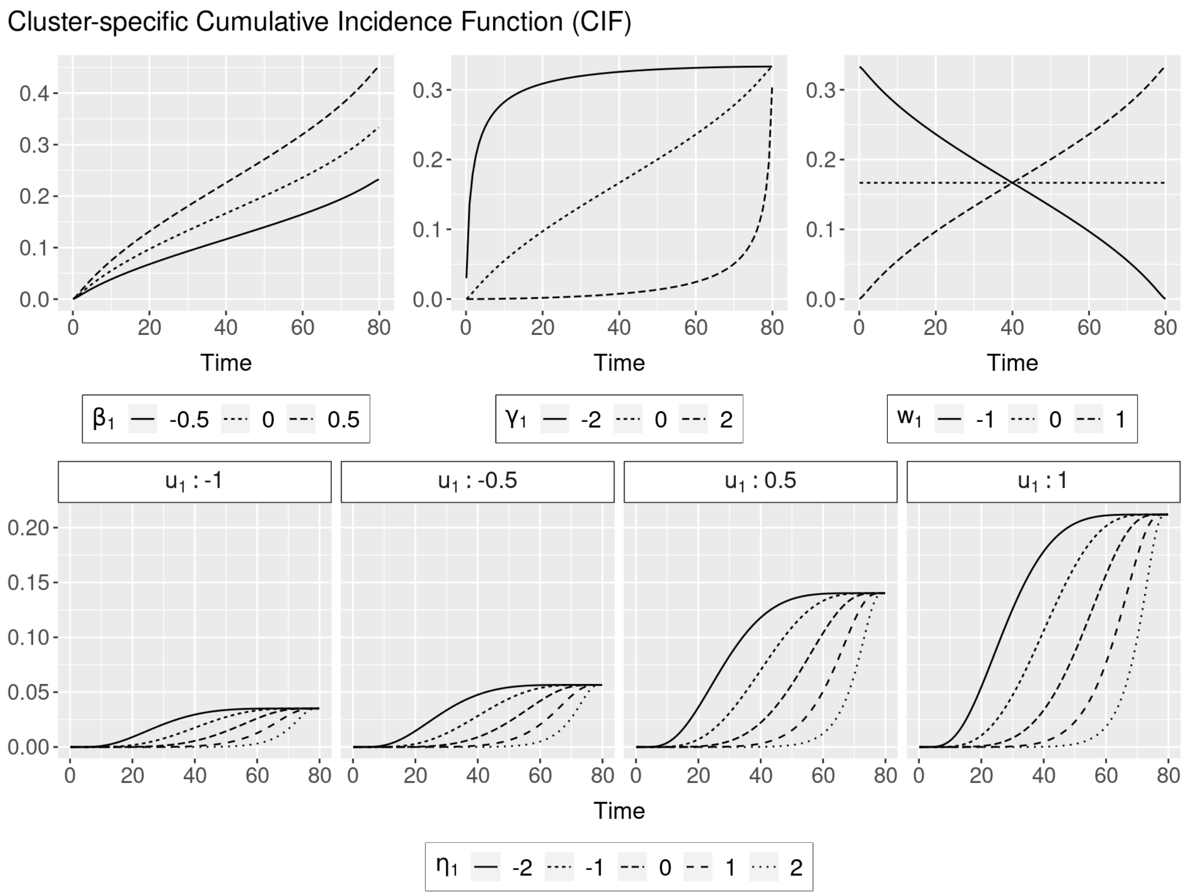

Figure 2: Curve behaviors for different parameter settings, showing then the corresponding parameter effects in a cluster-specific cumulative incidence function (CIF).

3 Estimation and inference

4 Simulation studies

5 Discussion

Supplementary material

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