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.

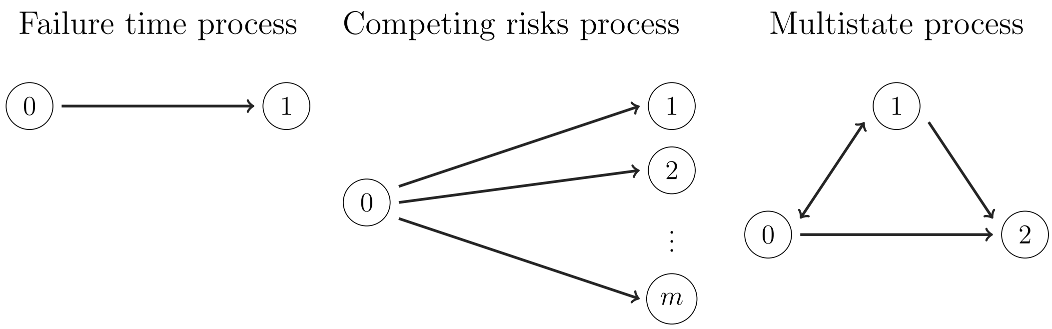

Figure 1: Illustration of failure time data layouts.

In the analysis of failure time data, the survival experiences are usually modeled in the hazard (failure rate) scale, and when the latent within-cluster dependence is accommodated we have the so-called frailty models (Prentice et al.; 1978; Clayton; 1978; Valpel et al.; 1979; Liang et al.; 1995; Petersen; 1998; Therneau and Grambsch; 2000). 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).

Parametric (Larson and Dinse; 1985) and semiparametric (Kuk; 1992) mixture model for competing risks data.

Besides, its inference is attached to the modeling scale, i.e. 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. There are some complicated

1. nonparametric approaches (Cheng et al.; 2007, 2009);
2. semiparametric approaches based on
    (a) composite likelihoods (Shih and Albert; 2009; Cederkvist et al.; 2019);
    (b) estimating equations (Scheike and Sun; 2012; Cheng and Fine; 2012);
    (c) copulas (Scheike et al.; 2010);
    (d) mixtures (Naskar et al.; 2005; Shi et al.; 2013);
3. linear transformation models (Fine; 1999; Gerds et al.; 2012).

The majority of them designed for bivariate CIFs,where increasing the CIF's dimension is a limitation.

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. In the case of longitudinal data, it is essential that the regression model take into account the longitudinal and/or grouped data structure.

According to Diggle et al. (2002) longitudinal data are repeated measures evaluated on the same subjects over time, that are potentially correlated. Dependent data can also arises in studies with block designs, spatial and multilevel data (Verbeke and Molenberghs; 2001; Fitzmaurice et al.; 2008). For the analysis of such data several methods have been proposed over the last four decades.

Laird and Ware (1982) proposed the random effects regression models for longitudinal data analysis. Breslow and Clayton (1993) presented the generalized linear mixed models (GLMMs) for the analysis of non-Gaussian outcomes. Masarotto and Varin (2012) developed a class of marginal models for modelling dependence structures in the analysis of longitudinal data, time series and spatial based on Gaussian copula models.

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

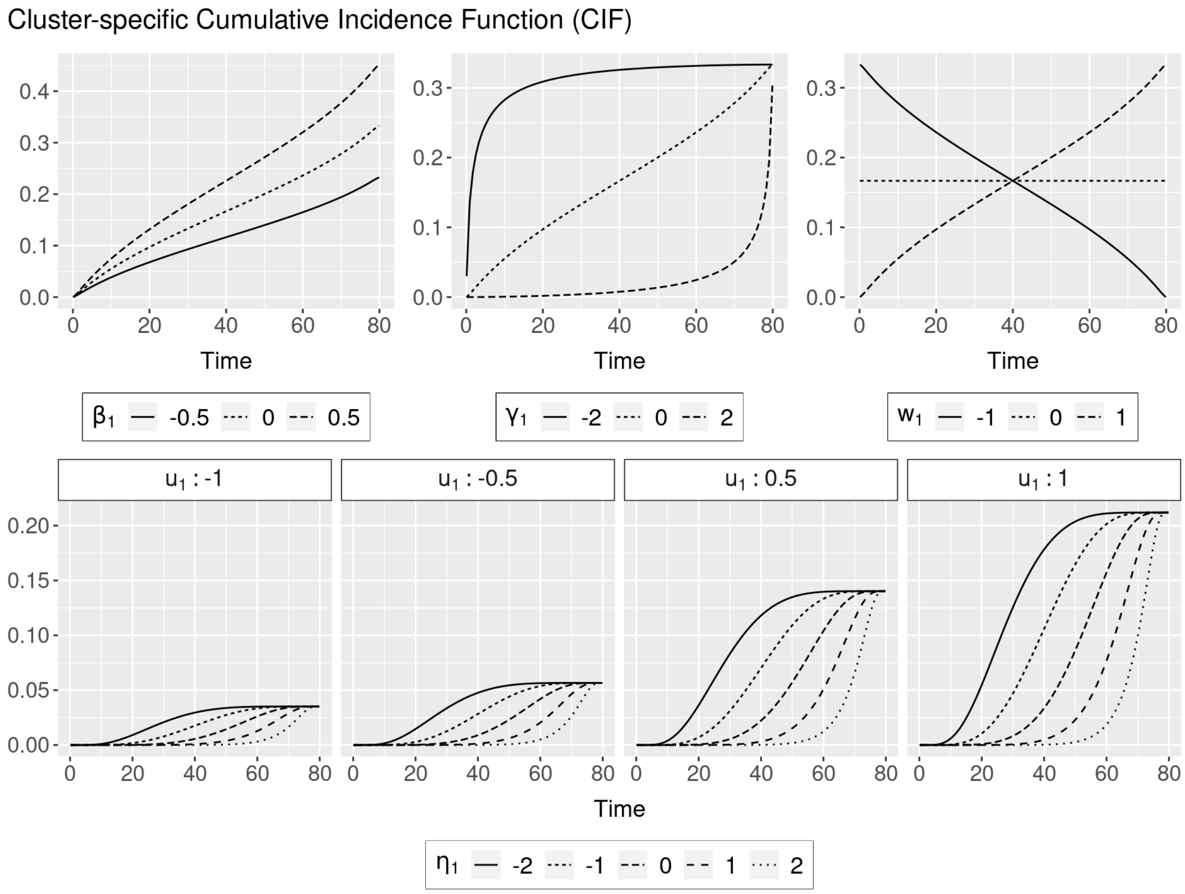

Figure 2: Curve behaviors for different parameter settings, showing then the corresponding parameter effects in a cluster-specific cumulative incidence function (CIF).

3 Estimation and inference

4 Simulation studies

5 Discussion

Supplementary material

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