Joint hierarchical generalized linear models with multivariate Gaussian random effects

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ARTICLE INFO

ABSTRACT

Likelihood based inference for correlated data involves the evaluation of a marginal likelihood integrating out random effects. In general this integral does not have a closed form. Moreover, its numerical evaluation might create difficulties especially when the dimension of random effects is high. *H*-likelihood inference has been proposed where the explicit evaluation of the integral is avoided. The approach also allows extensions handling e.g. (1) complex design experiments, (2) REML type of inference beyond the class of a linear model and (3) overdispersion modeling. The *h*-likelihood approach to multivariate generalized linear mixed models is extended. The *h*-likelihood computational algorithms is blended with a Newton–Raphson procedure for the estimation of the correlation parameters. This allows that components of the joint model are interlinked via correlated Gaussian random effects. Further, correlated random effects are allowed within each component. This approach can serve as a basis for further developments of joint double hierarchical generalized linear models with correlated random effects. The methods are illustrated with a rheumatoid arthritis study dataset, where the correlation between latent trajectories of three endpoints is evaluated.

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1. Introduction

The *h*-likelihood estimation technique originated in Lee and Nelder (1996). In that paper, the authors investigated the possibility to use the extended likelihood for estimation and inference of models with random effects. The special type of an extended likelihood where a random effect appears linearly in the linear predictor is called hierarchical likelihood or *h*-likelihood. We refer to Lee and Nelder (2005) for an extensive discussion of *h*-likelihood. In Lee and Nelder (1996) also the class of hierarchical generalized linear models (HGLM) class was defined. The HGLM is an extension of the generalized linear model (GLM) by adding random effects, which can follow any distribution from the conjugate Bayesian priors class.

In Lee and Nelder (1996) the authors proposed an augmented iterated weighted least squares algorithm (IWLS) to estimate the fixed and random effects from the hierarchical likelihood, given the variance components which are obtained from the adjusted profile likelihood. In a subsequent paper Lee and Nelder (2001a) developed a numerical procedure based on interlinked IWLS algorithms for fixed, random effects and variance components. This turned out to be a natural way for modeling dispersion or overdispersion parameters in a regression manner and Paula (2013) studied diagnostics for such models. Further it allowed the use of an extended quasi likelihood concept (Nelder and Pregibon, 1987). A further extension

of the algorithm was proposed in Noh and Lee (2007) for a less biased estimation of the fixed effects of a mean structure using an adjusted profile likelihood. These procedures were, however, developed for independent random effects.

Correlated random effects are discussed in Lee and Nelder (2001b). Correlation between the random components is essential in the definition of joint models, where components of the model are linked via correlated random effects. A bivariate binary–normal joined model was described in Yun and Lee (2004). Another joint model in the *h*-likelihood framework can be found in Ha et al. (2003) combining a time to event endpoint and a longitudinal Gaussian outcome. There the correlation between two models is handled by a shared random effect.

In this paper we present computational details of a joint hierarchical generalized linear model (JHGLM), where the number of endpoints may vary and follow the HGLM concept, and the correlations between random effects are estimated using a Newton–Raphson algorithm. Random effects are allowed to be correlated between the models as well as within a model. We applied the method to a rheumatoid arthritis data set, where it is of interest to replace one marker measured by a physician by self-reported markers. In this study we model jointly two binary outcomes and one Gaussian outcome. To further illustrate our computational method we also analyzed a bivariate simulated dataset, with a Poisson and Gaussian outcome as the first example, and a Poisson and binary outcome as the second example.

The paper is structured as follows. Section 2 describes the theory of a joint model and summarizes the *h*-likelihood method. Section 3 presents the estimation of a joint model in a *h*-likelihood framework. Section 4 applies the method to the rheumatoid arthritis study and two simulated datasets. In Section 5 concluding remarks are given. The Appendix contains details of the numerical computations.

2. Joint model

To analyze a longitudinal study with one endpoint the class of linear mixed models (LMM) or generalized linear mixed models (GLMM) can be used. *H*-likelihood estimation was first applied to responses of an exponential distribution blended with independent conjugate Bayesian random effects (Lee and Nelder, 1996, 2001a). This class of models constitutes the hierarchical generalized linear models (HGLM). HGLMs allow for overdispersion parameters to be included in the model. There are two different ways to model overdispersion in HGLMs (Lee and Nelder, 2000).

For a univariate HGLM the extended likelihood can be written as, see Lee et al. (2006):

$$L_E(\boldsymbol{\beta}, \boldsymbol{\lambda}, \mathbf{v}|\mathbf{y}, \mathbf{v}) = \prod_{i=1}^{N} \prod_{j=1}^{n_i} f_{\boldsymbol{\beta}, \boldsymbol{\lambda}}(y_{ij}|\mathbf{v}_i) f_{\boldsymbol{\lambda}}(\mathbf{v}_i), \qquad (2.1)$$

where y_{ij} is the observation of the *i*th subject ($i = 1 \ldots N$) at the *j*th time point ($j = 1 \ldots n_i$), $\boldsymbol{\beta}$ is the vector of fixed effects in the mean structure, $\mathbf{v}_i$ is the vector of latent random effects pertaining to the *i*th subject, and $\boldsymbol{\lambda}$ contains variances of the random effects and residual variances (overdispersion parameters) of the response. Parameter $\mathbf{v}$ appears in $L_E(\boldsymbol{\beta}, \boldsymbol{\lambda}, \mathbf{v}|\mathbf{y}, \mathbf{v})$ on the left hand side as unknowns to be estimated and on the right hand side as latent factors generating the data. A gentle introduction on the use of (2.1) in univariate HGLMs estimation can be found in Molas and Lesaffre (2011), where the method is also contrasted to the classical approach based on the marginal likelihood.

2.1. The joint HGLM

Now we write the *K* univariate longitudinal models as a joint HGLM (JHGLM) with the extended likelihood:

$$L_E(\boldsymbol{\beta}, \boldsymbol{\lambda}, \boldsymbol{\rho}, \mathbf{v}|\mathbf{y}, \mathbf{v}) = \prod_{i=1}^{N} \prod_{j=1}^{n_i} f_{\boldsymbol{\beta}, \boldsymbol{\lambda}}(y_{1ij}|\mathbf{v}_{1i}) \ldots f_{\boldsymbol{\beta}, \boldsymbol{\lambda}}(y_{kij}|\mathbf{v}_{ki}) \ldots f_{\boldsymbol{\beta}, \boldsymbol{\lambda}}(y_{Kij}|\mathbf{v}_{Ki}) f_{\boldsymbol{\lambda}}(\mathbf{v}_{1i}, \ldots, \mathbf{v}_{ki}, \ldots, \mathbf{v}_{Ki}). \qquad (2.2)$$

The above extended likelihood is a simple multiplication of univariate likelihoods in (2.1), and as such there is no difference whether the models (indexed by *k*) are fitted jointly or separately. Let $\boldsymbol{\beta} = (\boldsymbol{\beta}_1, \ldots, \boldsymbol{\beta}_k, \ldots, \boldsymbol{\beta}_K)^T$ and note that $\boldsymbol{\beta}_k$ is the specific parameter vector for *k*th univariate model, as also for $\boldsymbol{\lambda} = (\boldsymbol{\lambda}_1, \ldots, \boldsymbol{\lambda}_k, \ldots, \boldsymbol{\lambda}_K)^T$. Here we will consider the class of joint models as e.g. in Fieuws and Verbeke (2006), and impose a multivariate normal distribution on the latent variables:

$$f_{\boldsymbol{\lambda}}(\mathbf{v}_{1i}, \ldots, \mathbf{v}_{ki}, \ldots, \mathbf{v}_{Ki}) = \mathcal{MVN}_{\boldsymbol{\lambda}, \boldsymbol{\rho}}(\mathbf{v}_{1i}, \ldots, \mathbf{v}_{Ki}) \qquad (2.3)$$

where the vector $\boldsymbol{\lambda}$ represents the variance components and $\boldsymbol{\rho}$ represents the correlations of the joint multivariate normal distribution. To apply *h*-likelihood methods, the appropriate adjusted profile likelihoods of (2.2) must be used for estimation of $\boldsymbol{\lambda}$, $\boldsymbol{\rho}$ and $\boldsymbol{\beta}$. While the random effects are restricted to a normal distribution, the responses y_{kij} may have a distribution belonging to the exponential family i.e. normal, binomial, Poisson or gamma, possibly varying with *k*.

2.2. Estimation of fixed effects in the mean structure

In the general case, Noh and Lee (2007) suggest to work with a Laplace approximation to the marginal likelihood to estimate fixed effects in the mean structure. This involves the evaluation of the adjusted profile (log)-likelihood:

$$p_v(h) = h(\boldsymbol{\beta}, \boldsymbol{\lambda}, \boldsymbol{\rho}, \mathbf{v})|_{\mathbf{v}=\hat{\mathbf{v}}} - 0.5 \log \left| \frac{D(h, \mathbf{v})}{2\pi} \right|_{\mathbf{v}=\hat{\mathbf{v}}}, \qquad (2.4)$$