GLMMLasso: An Algorithm for High-Dimensional Generalized Linear Mixed Models Using ℓ_1 -Penalization

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Abstract

We propose an ℓ_1 -penalized algorithm for fitting high-dimensional generalized linear mixed models. Generalized linear mixed models (GLMMs) can be viewed as an extension of generalized linear models for clustered observations. Our Lasso-type approach for GLMMs should be mainly used as variable screening method to reduce the number of variables below the sample size. We then suggest a refitting by maximum likelihood based on the selected variables only. This is an effective correction to overcome problems stemming from the variable screening procedure which are more severe with GLMMs than for generalized linear models. We illustrate the performance of our algorithm on simulated as well as on real data examples. Supplemental materials are available online and the algorithm is implemented in the R package glmmixedlasso.

Key Words: coordinate gradient descent; Laplace approximation; random-effects model; variable selection.

1 Introduction

In recent years, high-dimensional linear regression models have been extensively studied. The most popular method to achieve sparse estimates is the Lasso (Tibshirani, 1996), which uses an ℓ_1 -penalty. The Lasso is not only attractive in terms of its statistical properties but also due to its fast computation solving a convex optimization problem. However, relatively few articles examine high-dimensional regression problems involving a non-convex loss function, i.e. Khalili and Chen (2007) and Städler et al. (2010) for Gaussian mixture models, Pan and Shen (2007) and Witten and Tibshirani (2010) for clustering and Witten and Tibshirani (2011) for linear discriminant analysis.

Generalized linear mixed models (McCullagh and Nelder, 1989; Breslow and Clayton, 1993; McCulloch and Searle, 2001; Molenberghs and Verbeke, 2005) are an extension of generalized linear models by adding random effects to the linear predictor in order to accommodate for clustered or overdispersed data. These models have received much attention in many applications such as biology, ecology, medicine, pharmaceutical science and econometrics. Available software packages (1me4 in R, NLMIXED in SAS, among others) allow to fit a wide range of generalized linear mixed models.

In this paper we develop a method for high-dimensional generalized linear mixed models. It is based on a Lasso-type regularization with a cyclic coordinate descent optimization. Due to shrinkage introduced by ℓ_1 -penalization, our approach performs in a first step variable screening, thereby selecting a set of candidate active variables. In other words, the proposed method primarily aims at reducing the dimensionality of the high-dimensional GLMM. In a second step, we perform refitting by maximum likelihood estimation to get accurate parameter estimates. The idea of such a two-stage approach has been used in linear models (Efron et al., 2004) and it is related to the adaptive Lasso (Zou, 2006) and the thresholded Lasso (Zhou, 2010; van de Geer et al., 2011). In fact, a two-stage approach is much more important than for linear models since shrinkage in GLMMs can have a severe effect on the estimation

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of variance components, see Sections 4 and 5.

To the best of our knowledge, there does not exist any literature devoted to truly high-dimensional generalized linear mixed models. Some papers focus on penalized variable selection procedures in generalized mixed models with low-dimensional data: we refer to Yang (2007), Ibrahim et al. (2010), Ni et al. (2010). Groll and Tutz (2012) have independently studied the same statistical problem and have also used a Lasso-type approach but with a focus on rather low-dimensional problems. Few papers focus on variable selection in generalized additive mixed models, for example Xue et al. (2010) and Lai et al. (2012). Schelldorfer et al. (2011) present statistical theory and an algorithm for high-dimensional Gaussian linear mixed models, where computation is much easier than in the generalized case.

The main contribution of the present paper is the construction and implementation of an efficient algorithm for ℓ_1 -penalization in truly high-dimensional generalized linear mixed models, called the GLMM-Lasso. We use the Laplace approximation (Bates, 2011b) and combine it with efficient coordinate gradient descent methods (Tseng and Yun, 2009). Our algorithm is feasible for problems where the number of variables is in the thousands and taking advantage of sparsity with respect to dimensionality (i.e. only few active variables) is exploited by an active set strategy.

The rest of the article is organised as follows. In Section 2, we review the generalized linear mixed model and introduce the GLMMLasso estimator. In Section 3, we describe the details of the computational algorithm before advocating the two-stage GLMMLasso estimators in Section 4. In Section 5 and 6 we consider the performance of our methods on simulated and real data sets. The article concludes with a discussion in Section 7. Supplemental materials including additional simulation examples are available online.

2 Generalized linear mixed models and ℓ_1 -penalized estimation

In this section, we first look at the classical GLMM setting where the number of observations is larger than the number of covariates, i.e. p < n. We closely follow Bates (2011a). Secondly, we consider the high-dimensional framework, i.e. $n \ll p$, and present the ℓ_1 -penalized maximum likelihood estimator.

2.1 Model formulation

Suppose that the observations are not independent but grouped instead. Let r = 1, ..., N be the grouping index and $j = 1, ..., n_r$ the jth outcome within group r. Denote by n the total number of observations, i.e. $n = \sum_{r=1}^{N} n_r$. Let \boldsymbol{X} be the $n \times p$ fixed-effects design matrix, \boldsymbol{Z} the $n \times q$ random-effects design matrix, $\boldsymbol{\mathcal{Y}}$ the n-dimensional random response vector and $\boldsymbol{\mathcal{B}}$ be the q-dimensional vector of random effects. We observe \boldsymbol{y} of $\boldsymbol{\mathcal{Y}}$ whereas $\boldsymbol{\mathcal{B}}$ is unobserved. The generalized linear mixed model is specified by the unconditional distribution of $\boldsymbol{\mathcal{B}}$ and the conditional distribution of $\boldsymbol{\mathcal{Y}}|\boldsymbol{\mathcal{B}}=\boldsymbol{b}$:

- i) $\mathcal{Y}_i | \mathbf{\mathcal{B}} = \mathbf{b}$ are independent for i = 1, ..., n.
- ii) The distribution of $\mathcal{Y}_i | \mathcal{B} = \mathbf{b}$ belongs to the exponential family with density

$$\exp\Big\{\phi^{-1}\Big(y_i\xi_i-b(\xi_i)\Big)+c(y_i,\phi)\Big\},\,$$

where b(.) and c(.,.) are known functions. ϕ is the dispersion parameter (known or unknown) and ξ_i is associated with the conditional mean $\mu_i := E[\mathcal{Y}_i | \mathcal{B} = \mathbf{b}]$, i.e. $\xi_i = \xi_i(\mu_i)$.

- iii) The conditional mean vector $\boldsymbol{\mu}$ depends on \boldsymbol{b} through the known link function g and the linear predictor $\boldsymbol{\eta} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{Z}\boldsymbol{b}$, with $\boldsymbol{\eta} = g(\boldsymbol{\mu})$ componentwise. Here, $\boldsymbol{\beta}$ is the unknown p-dimensional parameter vector, called fixed effects, and \boldsymbol{b} the unknown q-dimensional vector of random effects.
- iv) $\mathcal{B} \sim \mathcal{N}_q(\mathbf{0}, \Sigma_{\theta})$ where the covariance matrix Σ_{θ} is parameterized by the unknown parameter vector $\boldsymbol{\theta} \in \mathbb{R}^d$. We assume that Σ_{θ} is positive semidefinite, i.e. $\Sigma_{\theta} \geq 0$. The dimensionality d is typically small, say $d \leq 10$.

By using \mathcal{B} and Σ_{θ} in the definition above, we have already defined the random-effects structure of the GLMM. To be more precise, we have specified which variables have an additional random effect and how the structure of Σ_{θ} looks like (e.g. multiple of the identity or diagonal). A discussion of how to find these structures is beyond the scope of this paper.

Let us write Σ_{θ} in terms of its Cholesky decomposition $\Sigma_{\theta} = \Lambda_{\theta} \Lambda_{\theta}^{T}$ and introduce the (unobserved)

random variable \mathcal{U} defined by $\mathcal{B} := \Lambda_{\theta} \mathcal{U}$ where $\mathcal{U} \sim \mathcal{N}_q(\mathbf{0}, \mathbf{1}_q)$. Then the linear predictor $\boldsymbol{\eta}$ can be written as $\boldsymbol{\eta} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{Z}\Lambda_{\theta}\boldsymbol{u}$. We estimate the parameters $\boldsymbol{\beta}$, $\boldsymbol{\theta}$ and $\boldsymbol{\phi}$ (if unknown) by the maximum likelihood method and predict the random effects \boldsymbol{u} .

2.2 Likelihood function

Employing the notation $\xi_i(\mu_i) = \xi_i(\boldsymbol{\beta}, \boldsymbol{\theta})$, the likelihood function of a GLMM is given by the following expression:

$$L(\boldsymbol{\beta}, \boldsymbol{\theta}, \phi) = \int_{\mathbb{R}^q} \prod_{i=1}^n \left[\exp \left\{ \phi^{-1} \left(y_i \xi_i(\boldsymbol{\beta}, \boldsymbol{\theta}) - b(\xi_i(\boldsymbol{\beta}, \boldsymbol{\theta})) \right) + c(y_i, \phi) \right\} \right] \frac{1}{(2\pi)^{q/2}} \exp \left\{ -\frac{1}{2} \|\boldsymbol{u}\|_2^2 \right\} d\boldsymbol{u}$$

$$= \frac{1}{(2\pi)^{q/2}} \int_{\mathbb{R}^q} \exp \left\{ \sum_{i=1}^n \left(\frac{y_i \xi_i(\boldsymbol{\beta}, \boldsymbol{\theta}) - b(\xi_i(\boldsymbol{\beta}, \boldsymbol{\theta}))}{\phi} + c(y_i, \phi) \right) - \frac{1}{2} \|\boldsymbol{u}\|_2^2 \right\} d\boldsymbol{u}. \tag{1}$$

In general, the integral (1) can not be worked out analytically and numerical approximations are required, see Skrondal and Rabe-Hesketh (2004), Molenberghs and Verbeke (2005) and Jiang (2007).

2.3 The GLMMLasso estimator

We now turn to the high-dimensional setting where the number of fixed-effect variables p is much larger than the number of observations n, i.e. we study the so-called $n \ll p$ setup.

Let us assume that the true underlying fixed-effects vector $\boldsymbol{\beta}_0$ is sparse in the sense that many coefficients of $\boldsymbol{\beta}_0$ are zero. To enforce sparsity of our estimator, we advocate a Lasso-type approach. This means that we add an ℓ_1 -penalty for the fixed-effects vector $\boldsymbol{\beta}$ to the likelihood function. Thus, we are going to consider the following objective function:

$$Q_{\lambda}(\boldsymbol{\beta}, \boldsymbol{\theta}, \phi) = -2\log L(\boldsymbol{\beta}, \boldsymbol{\theta}, \phi) + \lambda \|\boldsymbol{\beta}\|_{1}, \tag{2}$$

where $\lambda \geq 0$ is a regularization parameter. Appropriate choices for λ are discussed in Section 4.

We aim at estimating the fixed-effect parameter $\boldsymbol{\beta}$, the covariance parameter $\boldsymbol{\theta}$, and if unknown the dispersion parameter ϕ , by

$$(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\theta}}, \hat{\boldsymbol{\phi}}) := \underset{\boldsymbol{\beta}, \boldsymbol{\theta}, \boldsymbol{\phi}}{\arg \min} Q_{\lambda}(\boldsymbol{\beta}, \boldsymbol{\theta}, \boldsymbol{\phi}). \tag{3}$$

We call (3) the GLMMLasso estimator. Since the likelihood function (1) comprises analytically intractable integrals (except for the Gaussian case), some approximations have to be used. We are going to illustrate the algorithm using the Laplace approximation. For GLMMs, it is accurate with low computational burden, as advocated by Bates (2011b). A thorough discussion of the accuracy and limitations of the Laplace approximation can be found in Joe (2008). Generally, the Laplace approximation is used to calculate integrals of the form

$$I = \int_{\mathbb{D}_a} e^{-S(\boldsymbol{u})} d\boldsymbol{u},\tag{4}$$

where S(u) is a known function of a q-dimensional variable u. Let

$$\tilde{\boldsymbol{u}} = \underset{\boldsymbol{u}}{\operatorname{arg\,max}} - S(\boldsymbol{u}) \tag{5}$$

(i.e. $S'(\tilde{u}) = 0$), then the Laplace approximation of I is given by

$$I \approx I^{LA} = (2\pi)^{q/2} |S''(\tilde{u})|^{-1/2} e^{-S(\tilde{u})}.$$
 (6)

The mode $\tilde{\boldsymbol{u}}$ in (5) is calculated by the penalized iterative least squares (PIRLS) algorithm. It is presented in Bates (2011b) and described in the supplemental materials. The PIRLS algorithm is related to the iterative reweighted least squares (IRLS) algorithm for obtaining the maximum likelihood estimator in generalized linear models.

It should be noted that $\tilde{\boldsymbol{u}}$ depends on $\boldsymbol{\beta}$, $\boldsymbol{\theta}$ and ϕ . From (1) and (6) we deduce that the Laplace approximation of the objective function $Q_{\lambda}(.)$ in (2) is

$$Q_{\lambda}^{LA}(\boldsymbol{\beta}, \boldsymbol{\theta}, \phi) = -2\sum_{i=1}^{n} \left\{ \frac{y_{i}\xi_{i}(\boldsymbol{\beta}, \boldsymbol{\theta}) - b(\xi_{i}(\boldsymbol{\beta}, \boldsymbol{\theta}))}{\phi} + c(y_{i}, \phi) \right\} + \log|(\boldsymbol{Z}\boldsymbol{\Lambda}_{\boldsymbol{\theta}})^{T}\boldsymbol{W}_{\boldsymbol{\beta}, \boldsymbol{\theta}, \phi}(\boldsymbol{Z}\boldsymbol{\Lambda}_{\boldsymbol{\theta}}) + \mathbf{1}_{q}|$$

$$+ \|\tilde{\boldsymbol{u}}(\boldsymbol{\beta}, \boldsymbol{\theta}, \phi)\|_{2}^{2} + \lambda \|\boldsymbol{\beta}\|_{1},$$

$$(7)$$

where $\mathbf{W}_{\boldsymbol{\beta},\boldsymbol{\theta},\phi} = \mathrm{diag}^{-1} \left(\phi v(\mu_i(\boldsymbol{\beta},\boldsymbol{\theta})) g'(\mu_i(\boldsymbol{\beta},\boldsymbol{\theta}))^2 \right)_{i=1}^n$ and v(.) is the known conditional variance function (McCullagh and Nelder, 1989). The estimator (3) is then approximated by

$$(\hat{\boldsymbol{\beta}}^{LA}, \hat{\boldsymbol{\theta}}^{LA}, \hat{\phi}^{LA}) := \underset{\boldsymbol{\beta}, \boldsymbol{\theta}, \boldsymbol{\phi}}{\arg\min} Q_{\lambda}^{LA}(\boldsymbol{\beta}, \boldsymbol{\theta}, \boldsymbol{\phi}). \tag{8}$$

We call (8) the GLMMLasso^{LA} estimator. It is the approximation (8) to the objective function (3) that is optimized to obtain the parameter estimates. Moreover, we would like to emphasize that (8) is a non-convex function with respect to (β, θ, ϕ) consisting of a non-convex loss function and a convex penalty.

3 Computational algorithm

In this section, we present the computational algorithm to obtain the GLMMLasso^{LA} estimator (8). The algorithm is based on ideas from Tseng and Yun (2009) of the (block) coordinate gradient descent (CGD) method. The notion of the CGD algorithm is that we cycle through components of the full parameter vector $\boldsymbol{\psi} := (\boldsymbol{\beta}, \boldsymbol{\theta}, \phi) \in \mathbb{R}^{p+d+1}$ and minimize the objective function $Q_{\lambda}^{LA}(.)$ only with respect to one parameter while keeping the other parameters fixed. In doing so we calculate a quadratic approximation and perform an indirect line search to ensure that the objective function decreases. (Block) CGD algorithms are used in Meier et al. (2008), Wu and Lange (2008), Friedman et al. (2010) and Breheny and Huang (2011) and are now extremely popular in high-dimensional penalized regression problems.

We first give an overview of the algorithm which solves minimization problem (8) exactly before considering an approximate algorithm which finds a solution close to the exact minimizer of (8). Finally, we present some details of the algorithm.

3.1 The exact GLMMLasso algorithm

We describe here an exact algorithm, called exact GLMMLasso (we notationally omit the involved Laplace approximation), for the Laplace approximated objective function in (8). Let us write (7) with a different notation to ease the presentation. For $\psi = (\beta, \theta, \phi) \in \mathbb{R}^{p+d+1}$, define the function

$$f(\boldsymbol{\psi}) := -2\sum_{i=1}^{n} \left\{ \frac{y_i \xi_i(\boldsymbol{\beta}, \boldsymbol{\theta}) - b(\xi_i(\boldsymbol{\beta}, \boldsymbol{\theta}))}{\phi} + c(y_i, \phi) \right\} + \log|(\boldsymbol{Z}\boldsymbol{\Lambda}_{\boldsymbol{\theta}})^T \boldsymbol{W}_{\boldsymbol{\psi}}(\boldsymbol{Z}\boldsymbol{\Lambda}_{\boldsymbol{\theta}}) + \mathbf{1}_q| + \|\tilde{\boldsymbol{u}}(\boldsymbol{\psi})\|_2^2.$$

Now (8) can be written as $\hat{\psi}_{\lambda}^{LA} = \arg\min_{\psi} Q_{\lambda}^{LA}(\psi) := f(\psi) + \lambda \|\beta\|_1$. Let e_j be the jth unit vector and denote by (s) the sth iteration step. Moreover, we let

$$\pmb{\beta}^{(s)} := (\beta_1^{(s)}, \dots, \beta_p^{(s)})^T, \quad \pmb{\theta}^{(s)} := (\theta_1^{(s)}, \dots, \theta_d^{(s)})^T, \quad \phi^{(s)}$$

be the estimates of β , θ and ϕ in the sth iteration. Using the notation

$$\boldsymbol{\beta}^{(s,s-1,\beta_k)} := \left(\beta_1^{(s)}, \dots, \beta_{k-1}^{(s)}, \beta_k, \beta_{k+1}^{(s-1)}, \dots, \beta_p^{(s-1)}\right)^T,$$

$$\boldsymbol{\theta}^{(s,s-1,\theta_l)} := \left(\theta_1^{(s)}, \dots, \theta_{l-1}^{(s)}, \theta_l, \theta_{l+1}^{(s-1)}, \dots, \theta_d^{(s-1)}\right)^T,$$

$$\boldsymbol{\beta}^{(s,s-1;k)} := \left(\beta_1^{(s)}, \dots, \beta_{k-1}^{(s)}, \beta_k^{(s-1)}, \beta_{k+1}^{(s-1)}, \dots, \beta_p^{(s-1)}\right)^T,$$

the exact GLMMLasso algorithm is summarized in Algorithm 1.

Particularly in the high-dimensional setting, the calculation of the quadratic approximation requires a large amount of computing time. Therefore it is interesting to examine a much faster approximate algorithm.

3.2 The (approximate) GLMMLasso algorithm

In the exact Algorithm 1 above, we consider in step (1) b) the mode $\tilde{\boldsymbol{u}}$ as a function of the parameters, i.e. $\tilde{\boldsymbol{u}} = \tilde{\boldsymbol{u}}(\boldsymbol{\beta}, \boldsymbol{\theta}, \phi)$. However, the calculation of the derivatives of f(.) with respect to β_k is computationally intensive. This becomes a major issue in the high-dimensional setting where a substantial amount of

Algorithm 1 Exact GLMMLasso algorithm

(0) Choose a starting value $\psi^{(0)} = (\boldsymbol{\beta}^{(0)}, \boldsymbol{\theta}^{(0)}, \phi^{(0)}).$

Repeat for $s = 1, 2, \dots$

- (1) (fixed-effect parameter optimization) For $k = 1, \dots, p$
 - a) (Laplace approximation)
 Calculate the Laplace approximation

$$Q_{\lambda}^{LA}\left(\boldsymbol{\beta}^{(s,s-1;k)},\boldsymbol{\theta}^{(s-1)},\phi^{(s-1)}\right).$$

- b) (Quadratic approximation and inexact line search)
 - i) Approximate the second derivative

$$\frac{\partial^2}{\partial \beta_{\scriptscriptstyle L}^2} f \Big(\pmb{\beta}^{(s,s-1,\beta_k)}, \pmb{\theta}^{(s-1)}, \phi^{(s-1)} \Big) \Big|_{\beta_k = \beta_{\scriptscriptstyle L}^{(s-1)}}$$

by $h_k^{(s)} > 0$ as described in the subsection below.

ii) Calculate the descent direction $d_k^{(s)} \in \mathbb{R}$

$$\begin{split} d_k^{(s)} := & \arg\min_{d} \Big\{ f\Big(\pmb{\beta}^{(s,s-1;k)}, \pmb{\theta}^{(s-1)}, \phi^{(s-1)} \Big) + \frac{\partial}{\partial \beta_k} f\Big(\pmb{\beta}^{(s,s-1,\beta_k)}, \pmb{\theta}^{(s-1)}, \phi^{(s-1)} \Big) \Big|_{\beta_k = \beta_k^{(s-1)}} d \\ & + \frac{1}{2} d^2 h_k^{(s)} + \lambda \| \pmb{\beta}^{(s,s-1;k)} + d \pmb{e}_k \|_1 \Big\}. \end{split}$$

iii) Choose a step size $\alpha_k^{(s)} > 0$ and set $\beta^{(s,s-1;k+1)} = \beta^{(s,s-1;k)} + \alpha_k^{(s)} d_k^{(s)} e_k$ such that

$$Q_{\lambda}^{LA}\Big(\boldsymbol{\beta}^{(s,s-1;k+1)},\boldsymbol{\theta}^{(s-1)},\boldsymbol{\phi}^{(s-1)}\Big) \leq Q_{\lambda}^{LA}\Big(\boldsymbol{\beta}^{(s,s-1;k)},\boldsymbol{\theta}^{(s-1)},\boldsymbol{\phi}^{(s-1)}\Big)$$

(2) (Covariance parameter optimization) For $l = 1, \ldots, d$

$$\boldsymbol{\theta}_{l}^{(s)} = \mathop{\arg\min}_{\boldsymbol{\theta}_{l}} Q_{\lambda}^{LA} \Big(\boldsymbol{\beta}^{(s)}, \boldsymbol{\theta}^{(s,s-1;\boldsymbol{\theta}_{l})}, \boldsymbol{\phi}^{(s-1)} \Big).$$

(3) (Dispersion parameter optimization)

$$\phi^{(s)} = \operatorname*{arg\,min}_{\phi} Q^{LA}_{\lambda} \Big(\pmb{\beta}^{(s)}, \pmb{\theta}^{(s)}, \phi \Big).$$

until convergence.

computing time is allocated to this particular part of the algorithm. In addition, the exact GLMMLasso algorithm requires a large number of outer iterations s. To attenuate these difficulties, we propose a slightly modified version of Algorithm 1. We suggest performing the quadratic approximation and the inexact line search while considering $\tilde{\boldsymbol{u}}$ as fixed and not depending on β_k . Denoting by $f(.|\tilde{\boldsymbol{u}})$ the function f(.) for which $\tilde{\boldsymbol{u}}$ is considered as fixed, the (approximate) GLMMLasso algorithm is given in Algorithm 2:

We illustrate in the supplemental materials that the approximate GLMMLasso algorithm speeds up remarkably without loosing that much accuracy. Additionally, the approximation emphasizes the importance of a refitting as advocated in the next section.

3.3 Convergence behaviour and details of the GLMMLasso algorithm

Numerical convergence. The convergence of the exact GLMMLasso algorithm to a stationary point can be proofed using the results presented in Tseng and Yun (2009). It is worth pointing out that in the low-dimensional framework, the exact GLMMLasso algorithm with $\lambda = 0$ (no penalization) gives the same results as the function glmer in the R package lme4.

- (0) Starting value $\psi^{(0)}$. As starting value for β , we fit a generalized linear model with the Lasso where the regularization parameter is chosen by cross-validation. The initial values for θ and ϕ are then calculated using steps (2) and (3) in Algorithm 1 and 2.
- i) Choice of $h_k^{(s)}$. For $h_k^{(s)}$ we choose the kth diagonal element of the Fisher information of a generalized linear model. Hence we use the second derivative of the first summand in (7). We set $c_{min} \leq h_k^{(s)} \leq c_{max}$

Algorithm 2 (Approximate) GLMMLasso algorithm

Denote by $\tilde{\boldsymbol{u}} = \tilde{\boldsymbol{u}}(\boldsymbol{\beta}^{(s,s-1;k)}, \boldsymbol{\theta}^{(s-1)}, \phi^{(s-1)})$. Replace in Algorithm 1 i) - iii) by

i') Approximate the second derivative

$$\frac{\partial^2}{\partial \beta_k^2} f\left(\boldsymbol{\beta}^{(s,s-1,\beta_k)}, \boldsymbol{\theta}^{(s-1)}, \phi^{(s-1)} \middle| \tilde{\boldsymbol{u}} \right) \Big|_{\beta_k = \beta_k^{(s-1)}}$$

by $h_k^{(s)} > 0$ as described in the subsection below.

ii') Calculate the descent direction $d_k^{(s)} \in \mathbb{R}$

$$\begin{split} \boldsymbol{d}_k^{(s)} &:= \arg\min_{\boldsymbol{d}} \Big\{ f\Big(\boldsymbol{\beta}^{(s,s-1;k)}, \boldsymbol{\theta}^{(s-1)}, \boldsymbol{\phi}^{(s-1)} \Big| \tilde{\boldsymbol{u}}\Big) + \frac{\partial}{\partial \beta_k} f\Big(\boldsymbol{\beta}^{(s,s-1,\beta_k)}, \boldsymbol{\theta}^{(s-1)}, \boldsymbol{\phi}^{(s-1)} \Big| \tilde{\boldsymbol{u}}\Big) \Big|_{\beta_k = \beta_k^{(s-1)}} \boldsymbol{d} \\ &+ \frac{1}{2} d^2 h_k^{(s)} + \lambda \|\boldsymbol{\beta}^{(s,s-1;k)} + d\boldsymbol{e}_k\|_1 \Big\}. \end{split}$$

iii') Choose a step size $\alpha_k^{(s)} > 0$ and set $\beta^{(s,s-1;k+1)} = \beta^{(s,s-1;k)} + \alpha_k^{(s)} d_k^{(s)} e_k$ such that

$$Q_{\lambda}^{LA}\Big(\boldsymbol{\beta}^{(s,s-1;k+1)},\boldsymbol{\theta}^{(s-1)},\boldsymbol{\phi}^{(s-1)}\big|\tilde{\boldsymbol{u}}\Big) \leq Q_{\lambda}^{LA}\Big(\boldsymbol{\beta}^{(s,s-1;k)},\boldsymbol{\theta}^{(s-1)},\boldsymbol{\phi}^{(s-1)}\big|\tilde{\boldsymbol{u}}\Big).$$

for positive constants c_{min} and c_{max} (e.g. $c_{min} = 10^{-5}$ and $c_{max} = 10^{5}$) in order that the algorithm converges (Tseng and Yun, 2009).

ii) Calculation of $d_k^{(s)}$. The value $d_k^{(s)}$ is the minimizer of the quadratic approximation of the objective function $Q_{\lambda}^{LA}(.)$ and analytically given by (Tseng and Yun, 2009)

$$d_{k}^{(s)} = \begin{cases} \operatorname{median} \left(\frac{\lambda - \partial/\partial \beta_{k} f_{\beta_{k}}}{h_{k}^{(s)}}, -\beta_{k}, \frac{-\lambda - \partial/\partial \beta_{k} f_{\beta_{k}}}{h_{k}^{(s)}} \right) & \text{if } \beta_{k} \text{ penalized} \\ -\frac{\partial/\partial \beta_{k} f_{\beta_{k}}}{h_{k}^{(s)}} & & \text{otherwise,} \end{cases}$$
(9)

where $f_{\beta_k} = f(\boldsymbol{\beta}^{(s,s-1;k)}, \boldsymbol{\theta}^{(s-1)}, \phi^{(s-1)})$ in Algorithm 1 and $f_{\beta_k} = f(\boldsymbol{\beta}^{(s,s-1;k)}, \boldsymbol{\theta}^{(s-1)}, \phi^{(s-1)}|\tilde{\boldsymbol{u}})$ in Algorithm 2.

iii) Choice of $\alpha_k^{(s)}$. The step length $\alpha_k^{(s)}$ is chosen such that the objective function $Q_{\lambda}^{LA}(.)$ decreases. We suggest to use the Armijo rule, which is defined for Algorithm 1 as follows (and correspondingly for Algorithm 2 with fixed $\tilde{\boldsymbol{u}}$):

Armijo rule: Choose $\alpha_k^{init} > 0$ and let $\alpha_k^{(s)}$ be the largest element of $\{\alpha_k^{init}\delta^l\}_{l=0,1,2,...}$ satisfying

$$Q_{\lambda}^{LA} \Big(\boldsymbol{\beta}^{(s,s-1;k)} + \alpha_{k}^{(s)} d_{k}^{(s)} \boldsymbol{e}_{k}, \boldsymbol{\theta}^{(s-1)}, \phi^{(s-1)} \Big) \leq Q_{\lambda}^{LA} \Big(\boldsymbol{\beta}^{(s,s-1;k)}, \boldsymbol{\theta}^{(s-1)}, \phi^{(s-1)} \Big) + \alpha_{k}^{(s)} \varrho \triangle^{k}$$

where
$$\triangle^k := \partial/\partial \beta_k f_{\beta_k} d_k^{(s)} + \gamma (d_k^{(s)})^2 h_k^{(s)} + \lambda \| \boldsymbol{\beta}^{(s,s-1;k)} + d_k^{(s)} \boldsymbol{e}_k \|_1 - \lambda \| \boldsymbol{\beta}^{(s,s-1;k)} \|_1.$$

The choice of the constants comply with the suggestions in Bertsekas (1999), e.g. $\alpha_k^{init}=1,\ \delta=0.5,\ \varrho=0.1$ and $\gamma=0.$

Active Set Algorithm. If we assume that the true fixed-effect parameter β_0 is sparse in the sense that many elements are zero, we can reduce the computing time remarkably by using an active set algorithm. This is also used in Meier et al. (2008) and Friedman et al. (2010). In particular, we only cycle through all p coordinates every Dth iteration, otherwise only through the current active set $S(\hat{\beta}^{(s-1)}) = \{k : \hat{\beta}_k^{(s-1)} \neq 0\}$. Typical values for D are 5 and 10.

An implementation of the algorithm is given in the R package glmmixedlasso and will be made available on R-Forge (http://r-forge.R-project.org/).

4 The two-stage GLMMLasso^{LA} estimator(s)

From the soft-thresholding property of the Lasso in linear models (Tibshirani, 1996) and in Gaussian linear mixed models (Schelldorfer et al., 2011), the fixed-effect estimate $\hat{\beta}$ is biased towards zero. In

some generalized linear mixed models the estimate of the covariance parameter θ is biased, too. To mitigate these bias problems and the approximation error induced by using the approximate GLMMLasso algorithm, we advocate a two-stage procedure. The first step aims at estimating a candidate set of predictors \hat{S} and can be seen as a variable screening procedure. The purpose of the second step is a more unbiased estimation of the parameters using unpenalized maximum likelihood (ML) estimation based on the selected variables \hat{S} from the first step. The proposed two-stage GLMMLasso algorithm is summarized in Algorithm 3:

Algorithm 3 Two-stage GLMMLasso algorithm

Stage 1: Compute the GLMMLasso^{LA} estimate (8) and the set \hat{S} .

Stage 2: Perform unpenalized ML estimation.

In the next subsections, we are going to discuss the specification of the set of variables \hat{S} . We propose two methods from the high-dimensional linear regression framework, and we do not consider the adaptive Lasso (Zou, 2006).

4.1 The GLMMLasso^{LA}-MLE hybrid estimator

The LARS-OLS hybrid estimator was examined in Efron et al. (2004) and also used in Meinshausen and Bühlmann (2006) and Meier et al. (2008). In our context, it becomes a two-stage procedure where the model is refitted including only the covariates with a nonzero fixed-effect coefficient in $\hat{\beta}_{init}$, where $(\hat{\beta}_{init}, \hat{\theta}_{init}, \hat{\phi}_{init})$ denotes the initial estimate from (8). More specifically, choose $\hat{S} = \hat{S}_{init} := \{k : |\hat{\beta}_{k,init} \neq 0\}$. Then the GLMMLasso^{LA}-MLE hybrid estimator is given by

$$(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\theta}}, \hat{\boldsymbol{\phi}})_{hybrid} := \underset{\boldsymbol{\beta}_{\hat{S}_{init}}, \boldsymbol{\theta}, \boldsymbol{\phi}}{\arg \min} -2 \log L(\boldsymbol{\beta}_{\hat{S}_{init}}, \boldsymbol{\theta}, \boldsymbol{\phi}), \tag{10}$$

where for $S \subseteq \{1, ..., p\}$, $(\beta_S)_k = \beta_k$ if $k \in S$ and $(\beta_S)_k = 0$ if $k \notin S$.

4.2 The thresholded GLMMLasso^{LA} estimator

The thresholded Lasso with refitting in high-dimensional linear regression models was examined in van de Geer et al. (2011) and Zhou (2010). We define the set \hat{S}_{thres} to be the set of variables which have initial fixed-effect coefficients larger than some threshold $\lambda_{thres} > 0$, i.e. we choose $\hat{S} = \hat{S}_{thres} := \{k : |\hat{\beta}_{k,init}| > \lambda_{thres}\}$. The thresholded GLMMLasso^{LA} estimator is then defined by

$$(\hat{\boldsymbol{\beta}}, \hat{\boldsymbol{\theta}}, \hat{\boldsymbol{\phi}})_{thres} := \underset{\boldsymbol{\beta}_{\hat{S}_{thres}}, \boldsymbol{\theta}, \boldsymbol{\phi}}{\arg \min} - 2 \log L(\boldsymbol{\beta}_{\hat{S}_{thres}}, \boldsymbol{\theta}, \boldsymbol{\phi}). \tag{11}$$

The thresholded GLMMLasso^{LA} estimator involves another regularization parameter λ_{thres} , which is determined by minimizing an information criterion presented in the next subsection.

4.3 Selection of the regularization parameters

Estimators (8), (10) and (11) require the choice of the regularization parameters λ and λ_{thres} , respectively. We propose to use the Bayesian Information Criterion (BIC) and the Akaike Information Criterion (AIC), defined by

$$c_{n,\lambda} = -2\log L(\hat{\beta}, \hat{\theta}, \hat{\phi}) + a(n) \cdot d\hat{f}_{\lambda}$$
(12)

where $a(n) = \log(n)$ for the BIC and a(n) = 2 for the AIC. Here, $\hat{df}_{\lambda} = |\{1 \le k \le p : \hat{\beta}_k \ne 0\}| + \dim(\hat{\theta})$ is the sum of the number of nonzero fixed-effect coefficients and the number of covariance parameters. The first summand is motivated by the work of Zou et al. (2007). The second summand is the approach of Bates (2010), who proposes that in the classical generalized mixed effects model the degrees of freedom are given by the number of unconstrained optimization parameters. Based on our empirical experience, we suggest for the estimators (8) and (10) the BIC, whereas for (11) we advocate using the AIC (allowing for a larger number of variables) to select λ first and then, sequentially, the BIC to select λ_{thres} . We will compare the performance of the three estimators in the next sections.

5 Simulation Study

In this section we assess the performance of the GLMMLasso^{LA} estimators (8), (10) and (11). We compare them with appropriate Lasso, maximum likelihood (ML) and Penalized Quasi-Likelihood (PQL, Breslow and Clayton (1993)) methods.

In the main text, we only present simulation results for the high-dimensional logistic mixed model. Simulation studies for the low-dimensional logistic and the Poisson mixed model are included in the supplementary material. At the end of this section, we compare the GLMMLasso LA estimates in a situation where the number of noise variables grows successively.

First of all, let us summarize some general conclusions drawn from real data analysis and the simulation studies:

- a) The variable screening performance of the GLMMLasso algorithm is not only attractive for the high-dimensional setting, but also for low-dimensional data with a relatively large number of variables (say p > 20).
- b) The GLMMLasso algorithm is numerically as stable as standard R functions like glmer (Bates, 2010) or glmmPQL (Breslow and Clayton, 1993; Venables and Ripley, 2002) when p < n. On the other hand, glmpath (Park and Hastie, 2007) and glmnet (Friedman et al., 2010) may fail to converge when high-dimensional models are misspecified.
- c) The main difference between the logistic and the Poisson mixed model is the shrinkage of the covariance parameter estimates of the $GLMMLasso^{LA}$ estimator. These estimates are severely biased in logistic mixed models, in contrast to the Poisson mixed model. Further differences between these two classes are summarized in the supplemental materials.
- d) The number of iterations s substantially differs between the classes of generalized linear mixed models and the data set.

5.1 Preview for the logistic mixed model

In this section we confine the discussion to the logistic mixed model because it is viewed as the most challenging model within the class of generalized linear mixed models (Molenberghs and Verbeke, 2005; Jiang, 2007). As an overview, let us sum up the main findings from the simulation study in the logistic mixed model:

- i) The GLMMLasso^{LA} estimate from (8) of the covariance parameter $\boldsymbol{\theta}$ is notably biased. In other words, adding an ℓ_1 -penalty does not only shrink the fixed effects estimate $\hat{\boldsymbol{\beta}}$, but also the covariance parameter estimate $\hat{\boldsymbol{\theta}}$.
- ii) In the high-dimensional settings, the GLMMLasso^{LA}-MLE hybrid estimator (10) performs better in terms of parameter estimation accuracy than the thresholded GLMMLasso^{LA} estimator (11).
- iii) The more random effects, the more important it is to use the GLMMLasso LA for variable screening (instead of a Lasso ignoring the grouping structure).
- iv) The number of total iterations s needed is small, often about 15 iterations.

5.2 High-dimensional logistic mixed model

In all subsequent simulation schemes (including the supplemental materials), we restrict ourselves to the case where the number of observations per cluster is equal, i.e. $n_r = n_C$ for r = 1, ..., N. The covariates are generated from a multivariate normal distribution with mean zero and covariance matrix V with pairwise correlation $V_{kk'} = \rho^{|k-k'|}$ and $\rho = 0.2$. Denote by β_0 the true fixed effects (wherein $(\beta_0)_1$ is the intercept) and by s_0 the true number of nonzero fixed-effect coefficients.

For the logistic mixed models, the intercept and the first covariate have independent random effects with different variance parameters. In particular, $\boldsymbol{\theta} = (\theta_1, \theta_2)$ and covariance matrix $\boldsymbol{\Sigma}_{\boldsymbol{\theta}} = \operatorname{diag}(\theta_1^2, \dots, \theta_1^2, \theta_2^2, \dots, \theta_2^2) \in \mathbb{R}^{2N}$, i.e. q = 2N. We investigate the following two examples in the high-dimensional setting:

$$H_1$$
: $N = 40$, $n_C = 10$, $n = 400$, $p = 500$, $\theta_1^2 = \theta_2^2 = 1$ and $s_0 = 5$ with $\boldsymbol{\beta}_0 = (0.1, 1, -1, 1, -1, 0, \dots, 0)^T$. H_2 : $N = 50$, $n_C = 10$, $n = 500$, $p = 1500$, $\theta_1^2 = \theta_2^2 = 1$ and $s_0 = 5$ with $\boldsymbol{\beta}_0 = (0.1, 1, -1, 1, -1, 0, \dots, 0)^T$.

The fitted models are all correctly specified. Hereafter, we denote by oracle the ML estimate of the model which includes only the variables from the true active set. Let glmmlasso, hybrid glmmlasso and thres glmmlasso be the GLMMLasso^{LA} estimates (8), (10) and (11), respectively. We compare the GLMMLasso^{LA} methods with the standard Lasso for generalized linear models (which ignore the grouping structure). For that purpose we use the glmpath algorithm (Park and Hastie, 2007) and the BIC as variable selection criterion. Then, let hybrid glmpath and thres glmpath be the two-stage procedures based on glmpath (without random effects).

The results in the form of median and rescaled median absolute deviation (in parentheses) over 100 simulation runs are shown in Table 1. There, $|S(\hat{\beta})|$ denotes the cardinality of the estimated active set and TP is the number of true positives (selected variables which are in the true active set). SE is the squared error of the fixed-effect coefficients, i.e. $SE = ||\hat{\beta} - \beta_0||_2^2$.

Table 1: Simulation results (medians) for the logistic mixed models H_1 and H_2 (rescaled median absolute deviations in parentheses). A * means that the corresponding coefficient is not subject to penalization in the GLMMLasso^{LA} estimate.

Model	Method	$ S(\hat{\boldsymbol{\beta}}) $	TP	$\hat{\theta}_1^2$	$\hat{ heta}_2^2$	\hat{eta}_1^*	\hat{eta}_2^*	Âa	\hat{eta}_4	\hat{eta}_5	SE
True	Method	$\frac{ \mathcal{D}(\mathcal{P}) }{5}$	5	1 1	$\frac{v_2}{1}$	$\frac{\rho_1}{0.1}$	$\frac{\rho_2}{1}$	$\frac{\hat{\beta}_3}{-1}$		-1	DE
True		9	9	1	1	0.1	1	-1	1	-1	
H_1	oracle	5	5	0.85	0.86	0.07	1.04	-0.99	0.98	-1.01	0.14
1		(0)	(0)	(0.4)	(0.59)	(0.2)	(0.25)	(0.22)	(0.18)	(0.14)	(0.088)
	glmmlasso	6	5	0.38	0.37	0.06	0.66	-0.3	$0.26^{'}$	-0.34	1.6
		(1.48)	(0)	(0.24)	(0.3)	(0.14)	(0.16)	(0.14)	(0.14)	(0.12)	(0.42)
	glmpath	7	5	-	-	$0.04^{'}$	$0.24^{'}$	-0.21	$0.22^{'}$	-0.28	2.4
	0 1	(2.22)	(0)	_	_	(0.13)	(0.12)	(0.11)	(0.1)	(0.1)	(0.52)
	hybrid glmmlasso	6	5	0.89	0.87	0.08	$1.05^{'}$	-0.99	1	-1.03	$0.44^{'}$
		(1.48)	(0)	(0.43)	(0.58)	(0.19)	(0.25)	(0.23)	(0.18)	(0.16)	(0.32)
	hybrid glmpath	7	5	0.86	$0.87^{'}$	0.08	1.01	-0.99	0.99	-1.02	$0.7^{'}$
		(2.22)	(0)	(0.42)	(0.53)	(0.2)	(0.28)	(0.24)	(0.19)	(0.16)	(0.64)
	thres glmmlasso	10	5	1.02	1.11	0.1	1.19	-1.09	1.11	-1.13	1.3
		(3.71)	(0)	(0.7)	(0.85)	(0.22)	(0.29)	(0.23)	(0.2)	(0.19)	(0.77)
	thres glmpath	10	5	0.91	0.94	0.09	1.11	-1.07	1.11	-1.1	1.1
		(2.97)	(0)	(0.49)	(0.59)	(0.21)	(0.27)	(0.25)	(0.19)	(0.2)	(0.73)
H_2	oracle	5	5	0.89	0.94	0.11	1.02	-0.98	1.02	-1.02	0.13
		(0)	(0)	(0.4)	(0.53)	(0.18)	(0.25)	(0.15)	(0.18)	(0.16)	(0.1)
	glmmlasso	6	5	0.39	0.41	0.09	0.66	-0.31	0.27	-0.34	1.6
		(1.48)	(0)	(0.23)	(0.28)	(0.13)	(0.17)	(0.1)	(0.11)	(0.09)	(0.27)
	glmpath	6.5	5	-	-	0.08	0.23	-0.21	0.21	-0.28	2.4
		(0.74)	(0)	-	-	(0.11)	(0.13)	(0.08)	(0.11)	(0.08)	(0.34)
	hybrid glmmlasso	6	5	0.93	0.96	0.12	1.02	-0.99	1.05	-1.04	0.34
		(1.48)	(0)	(0.44)	(0.51)	(0.19)	(0.26)	(0.15)	(0.17)	(0.16)	(0.3)
	hybrid glmpath	6.5	5	0.87	0.94	0.12	1.01	-0.99	1.03	-1.04	0.48
		(0.74)	(0)	(0.42)	(0.5)	(0.18)	(0.22)	(0.15)	(0.18)	(0.17)	(0.37)
	thres glmmlasso	14	5	1.3	1.33	0.16	1.26	-1.16	1.2	-1.22	2
		(5.93)	(0)	(0.87)	(0.79)	(0.27)	(0.27)	(0.28)	(0.26)	(0.24)	(1.7)
	thres glmpath	13.5	5	0.9	1.03	0.17	1.17	-1.07	1.13	-1.15	1.8
		(5.19)	(0)	(0.52)	(0.64)	(0.24)	(0.25)	(0.19)	(0.22)	(0.21)	(1.2)

Comparing the cardinality of the active set, we see that thres glmmlasso and thres glmpath have much larger active sets than glmmlasso and glmpath, respectively. This is largely due to the fact that we employ the AIC in the first and the BIC in the second stage. This is outweighed by the advantage that on average (not shown), the true effects are predominantly included in thres glmmlasso. The active set of glmmlasso is slightly smaller than that of glmpath. And yet, the number of TP is similar as for glmpath. Hence, we conclude that the existence of random effects does affect the variable selection performance of glmpath.

Concerning covariance parameter estimation, we read off from the table that $\hat{\theta}_1^2$ and $\hat{\theta}_2^2$ are seriously biased for *glmmlasso*. This motivates the usage of a two-stage procedure. The table suggests that the hybrid and the thresholded procedures have improved estimation accuracy of the random effects parameters compared to their original counterparts.

Looking at the fixed-effect parameter estimation accuracy, the simulation study reveals that the *glmmlasso* estimates are less biased than the corresponding *glmpath* estimates, resulting in lower squared error. And the same holds for *hybrid glmmlasso* and *hybrid glmpath*. The fixed-effect parameter estimates

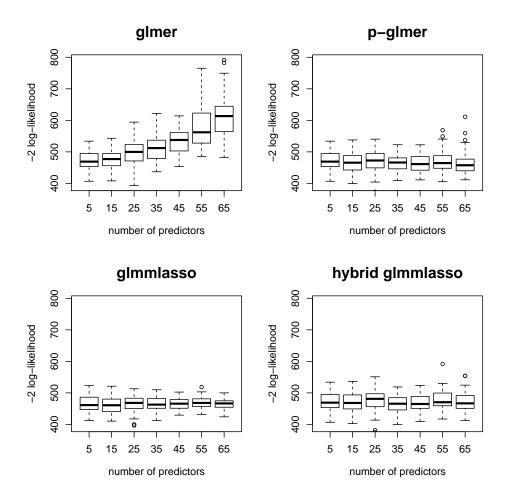


Figure 1: Minus twice out-of-sample log-likelihood for a growing number of covariates. The ML estimate performs badly whereas the $GLMMLasso^{LA}$ estimators remain stable, and they are comparable to the p-glmer in the low-dimensional framework.

of thres glmmlasso and thres glmpath perform inadequately compared to their hybrid counterparts. As marked by an asterisk in the table, β_2 is not subject to penalization for the GLMMLasso^{LA} estimator since this variable has a random effect (Schelldorfer et al., 2011). Thus the bias of the estimate is much smaller than for the other fixed-effect coefficients.

To sum up the simulation study, we first conclude that *hybrid glmmlasso* outperforms *thres glmmlasso* in terms of parameter estimation accuracy, with similar performance regarding true positives. Second, *glmmlasso* procedures do outperform *glmpath* procedures as variable screening methods. Of course, *glmpath* is fitting a wrong model without random effects.

5.3 Logistic mixed model with a growing number of noise covariates

Here, we assess the performance of glmmlasso and hybrid glmmlasso when the number of noise variables grows successively. In the low-dimensional setting, we compare them with the ML estimate computed by the R function glmer (denoted by glmer). In addition, let p-glmer be the method which performs variable selection in the following way: Eliminate consecutively (backward selection) all variables with a p-value larger than 5% until the final model is attained comprising only significant variables. We compare these four methods in terms of their performance of twice the negative out-of-sample log-likelihood. Let us fix the following random intercept model design: n = 400, N = 40, $n_C = 10$, $\theta^2 = 1$, $\theta_0 = (0, 1, -1, 1, -1)$. We start with p = 5 (no noise variables) and raise the number of variables to p = 65. The results over 50 simulation runs are depicted in Figure 1.

The figures show that the negative out-of-sample log-likelihood values for glmer grow polynomial whereas the likelihoods for the other methods remain fairly constant. The increase in glmer stems from

the fact that it overfits the model for a growing number of covariates. When focusing on the figures in more detail, we read off that the negative log-likelihood of glmmlasso increases slightly for larger p whereas the negative log-likelihood of $hybrid\ glmmlasso$ remains stable. The rationale for this small increase in glmmlasso is that the more noise covariates, the larger the optimal λ , and henceforth the larger the shrinkage of the fixed effects. And this leads to the increase of the out-of-sample log-likelihood. $hybrid\ glmmlasso$ (and also $thres\ glmmlasso$) overcomes this problem and leads to a stable out-of-sample log-likelihood irrespective of p.

5.4 Correlated Random Effects

Both from a methodological and an implementational point of view it is conceptually possible to use correlated random effects. As an illustration we use the logistic mixed model H_1 with correlated random effects (with unstructured covariance matrix) where we use a correlation of $\rho = 0.5$ between the two random effects. The corresponding results are illustrated in Table 2. The results are very similar to the uncorrelated case. However, the bias of the correlation estimate seems to be less severe than the bias of the variance components.

Table 2: Simulation results (medians) for the logistic mixed models H_1 (rescaled median absolute deviations in parentheses). A * means that the corresponding coefficient is not subject to penalization in the $GLMMLasso^{LA}$ estimate.

Model	Method	$ S(\hat{\boldsymbol{\beta}}) $	TP	$\hat{ heta}_1^2$	$\hat{ heta}_2^2$	ρ̂	\hat{eta}_1^*	\hat{eta}_2^*	\hat{eta}_3	\hat{eta}_4	\hat{eta}_5	SE
True		5	5	1	1	0.5	0.1	1	-1	1	-1	
H_1	oracle	5	5	0.88	0.94	0.53	0.1	0.97	-1.03	1.02	-1.01	0.14
	glmmlasso	(0) 6	$ \begin{array}{c} (0) \\ 5 \end{array} $	(0.46) 0.41	$(0.54) \\ 0.41$	$(0.37) \\ 0.63$	$(0.18) \\ 0.07$	(0.24) 0.66	(0.17) -0.33	(0.15) 0.28	(0.15) -0.34	$(0.1) \\ 1.6$
	G	(1.48)	(0)	(0.22)	(0.25)	(0.51)	(0.14)	(0.16)	(0.12)	(0.11)	(0.11)	(0.35)

6 Illustration

In this section we illustrate the proposed $GLMMLasso^{LA}$ estimators for Poisson regression on an extended real data set with count data.

Data description. We consider the epilepsy data from Thall and Vail (1990) which were also analyzed by Breslow and Clayton (1993). The data were obtained from a randomized clinical trial of 59 patients with epilepsy, comparing a new drug (Trt=1) with placebo (Trt=0). The response variable consists of counts of epileptic seizures during the two weeks before each of four clinic visits (V4=1 for fourth visit, 0 otherwise). Further covariates in the analysis are the logarithm of age (Age), the logarithm of 1/4 the number of baseline seizures (Base) and the interaction of Base and Trt (Base x Trt). The main question of interest is whether taking the new drug reduces the number of epileptic seizures compared with placebo. In order to assess the performance of the proposed procedure with high-dimensional data, we add U(-1,1) distributed noise predictors to get a data set with n=236, N=59, $n_r=4$ for $r=1,\ldots,N$ and p=4000. All predictors are standardized to have mean zero and standard deviation one.

Model. Model III in Breslow and Clayton (1993) is a two level GLMM (Bates, 2010), which is an extension of the single level GLMM introduced in Section 2 for more than one grouping variable. The model consists of two independent random intercept effects. One for subject (level 1, index r) and one for observation (level 2, index j). Let θ_{sub}^2 and θ_{obs}^2 be the corresponding variance parameters. Then the linear predictor can be written as

$$\log(\mu_{rj}) = \eta_{rj} = \boldsymbol{x}_{rj}^T \boldsymbol{\beta} + \theta_{sub} u_r + \theta_{obs} u_{rj} \quad r = 1, \dots, 59, \quad j = 1, \dots, 4.$$

Results. The results of the analysis are presented in Table 3. In the first column we show the estimates for Model III without performing variable selection. There, Intercept, Base and Trt are significant at the 5% level (indicated by †). If we perform backward selection using the BIC, we end up with a model including Intercept and Base only. And this model coincides with the one selected by glmmlasso. Hybrid

glmmlasso overcomes the bias problems of glmmlasso and it yields a better model in terms of the BIC. Thres glmmlasso includes additional noise variables, thereby achieving the smallest BIC score for all models under consideration. Comparing hybrid glmmlasso and thres glmmlasso, the table suggests that the additional covariates in the latter model reduce the variability while keeping the fixed-effect estimates unaltered.

Table 3: Results for the epilepsy data. Model III is based on 6 fixed-effect covariates while the other methods are based on p = 4000 variables, including 3994 noise covariates. † indicates that the corresponding coefficient is significant at the 5% level. † means that five noise variables are selected, but not shown in the table. $S(\hat{\beta}) = \{k : \hat{\beta}_k \neq 0\}$ is the total number of selected variables.

	Model III	glmmlasso	hybrid glmmlasso	thres glmmlasso
BIC	527.3	571.8	515.5	480.3
$S(\hat{\boldsymbol{\beta}})$	6	2	2	7^{\ddagger}
Intercept	1.58^{\dagger}	1.62	1.58	1.58
Base	0.66^{\dagger}	$< 10^{-4}$	0.74	0.75
Trt	-0.47^\dagger	-	-	-
Base x Trt	0.36	-	-	-
Age	0.11	-	-	-
V4	-0.04	-	-	-
$\hat{\theta}_{sub}^2$	0.21	0.68	0.25	0.28
$\begin{array}{c} \hat{\theta}_{sub}^2 \\ \hat{\theta}_{obs}^2 \end{array}$	0.13	0.12	0.13	0.04

7 Concluding Remarks

We address the problem of estimating high-dimensional generalized linear mixed models (GLMMs). While low-dimensional generalized linear mixed models (Bates, 2010) and high-dimensional generalized linear models (van de Geer, 2008) have been extensively studied in recent years, little attention has been devoted to high-dimensional GLMMs. We provide an efficient algorithm for the ℓ_1 -penalized maximum likelihood estimator, called GLMMLasso. It is based on the Laplace approximation, coordinatewise optimization and a speeding up approximation. The method should be typically used as a screening procedure to estimate a small set of important variables. We propose refitting by maximum likelihood to get accurate parameter estimates. The second stage is much more important than for linear models, because ℓ_1 -shrinkage can lead to severe bias problems for the estimation of the variance components. Our work is primarily a contribution addressing the numerical challenges of performing high-dimensional variable selection and parameter estimation in nonlinear mixed-effects models involving a non-convex loss function. An implementation of the algorithm can be found in our R package glmmixedlasso. It will be made available on R-Forge.

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"GLMMLasso: An Algorithm for High-Dimensional Generalized Linear Mixed Models Using ℓ_1 -Penalization"

Jürg Schelldorfer, Lukas Meier and Peter Bühlmann

Appendix A: PIRLS algorithm

In this section, we explain how to determine the mode $\tilde{\boldsymbol{u}} = \arg\max_{\boldsymbol{u}} -S(\boldsymbol{u})$ (introduced in Section 2 of the article). We have to solve the following minimization problem:

$$\tilde{\boldsymbol{u}} = \arg\min_{\boldsymbol{u}} S(\boldsymbol{u}) := -\sum_{i=1}^{n} \left\{ \frac{y_i \xi_i(\boldsymbol{u}) - b(\xi_i(\boldsymbol{u}))}{\phi} + c(y_i, \phi) \right\} + \frac{1}{2} \|\boldsymbol{u}\|_2^2.$$
(13)

We would like to highlight that S(u) is a convex function. We employ the Newton-Raphson algorithm to find a global minimum. From (13) we get

$$S'(u) = -(Z\Lambda_{\theta})^T B(y - \mu) + u$$
, $S''(u) = (Z\Lambda_{\theta})^T W(Z\Lambda_{\theta}) + 1_q$

where $\mathbf{W} = \operatorname{diag}^{-1} \left(\phi v(\mu_i) g'(\mu_i)^2 \right)_{i=1}^n$, $\mathbf{B} = \operatorname{diag}^{-1} \left(\phi v(\mu_i) g'(\mu_i) \right)_{i=1}^n$ and v(.) is the conditional variance function (McCullagh and Nelder, 1989). Then following the lines in Hastie et al. (2009), we get Algorithm 4, which is also described in Bates (2011a) and Bates (2011b).

Algorithm 4 PIRLS algorithm

Choose a starting value or set $\mathbf{u}^{(0)} = 0$.

Repeat for r = 0, 1, 2, ...

$$\begin{split} & \boldsymbol{\eta}^{(r)} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{Z}\boldsymbol{\Lambda}_{\boldsymbol{\theta}}\boldsymbol{u}^{(r)} \\ & \boldsymbol{\mu}^{(r)} = g^{-1}(\boldsymbol{\eta}^{(r)}) \\ & \boldsymbol{W}^{(r)} = \operatorname{diag}\left(\frac{1}{\phi v(\mu_i^{(r)})g'(\mu_i^{(r)})^2}\right)_{i=1}^n \boldsymbol{G}^{(r)} = \operatorname{diag}\left(\phi v(\mu_i^{(r)})g'(\mu_i^{(r)})^2\right)_{i=1}^n \\ & \boldsymbol{B}^{(r)} = \operatorname{diag}\left(\frac{1}{\phi v(\mu_i^{(r)})g'(\mu_i^{(r)})}\right)_{i=1}^n \\ & \boldsymbol{z}^{(r)} = (\boldsymbol{Z}\boldsymbol{\Lambda}_{\boldsymbol{\theta}})\boldsymbol{u}^{(r)} + \boldsymbol{G}^{(r)}\boldsymbol{B}^{(r)}(\boldsymbol{y} - \boldsymbol{\mu}^{(r)}) \end{split}$$

Then solve

$$\left((\boldsymbol{Z}\boldsymbol{\Lambda}_{\boldsymbol{\theta}})^T\boldsymbol{W}^{(r)}(\boldsymbol{Z}\boldsymbol{\Lambda}_{\boldsymbol{\theta}}) + \boldsymbol{1}_q\right)\boldsymbol{u}^{(r+1)} = (\boldsymbol{Z}\boldsymbol{\Lambda}_{\boldsymbol{\theta}})^T\boldsymbol{W}^{(r)}\boldsymbol{z}^{(r)}$$

until

$$\frac{\|\boldsymbol{\eta}^{(r+1)} - \boldsymbol{\eta}^{(r)}\|_2}{\|\boldsymbol{\eta}^{(r)}\|_2} \le tol$$
.

Set $\tilde{\boldsymbol{u}} = \boldsymbol{u}^{(r+1)}$.

The PIRLS algorithm typically converges fast. To further speed up Algorithm 1 and 2, we use the current value of \tilde{u} as starting value in step (1) a) of Algorithm 1. Consequently, the number of iterations required to update \tilde{u} is indeed small, often smaller than three.

Appendix B: Comparison of the exact and approximate GLMM-Lasso algorithm

In this section, we compare the exact and the approximate algorithm (i.e. Algorithm 1 and 2) on various simulated data sets. We use the same model settings as in the simulation studies (see Section 5 of the main article and Appendices C and D).

First of all, let us give an overview of the key findings about the approximate version of the algorithm:

- 1. The approximate algorithm is substantially faster than the exact algorithm (often more than 50%).
- 2. For the logistic mixed model, the loss in accuracy (with respect to variable selection and parameter estimation) is very small.
- 3. For the Poisson mixed model, the loss in accuracy stems from the selection of too many covariates with very small fixed-effects coefficients. This problem is effectively alleviated by the proposed two-stage procedures (see Section 4).

In detail, we compare the algorithms in terms of computing time, number of iterations, likelihood function, the active set and the fixed-effects estimation accuracy. Denote by x^e the measure for the exact and x^a the corresponding measure for the approximate GLMMLasso algorithm. Precisely, let $rel.time = t^a/t^e$ be the relative (cpu) time, $rel.iter = Iter^a/Iter^e$ be the relative number of outer iterations s, $rel.ll = |\ell^a - \ell^e|/|\ell^e|$ the relative difference of the likelihood function values, $rel.fix = ||\beta^a - \beta^e||_2/||\beta^e||_2$ be the relative difference of the fixed-effects parameters and activeSet the percentage of models where the active sets completely coincide for the exact and the approximate algorithm. For each model, we carry out 50 simulation runs. And for each run, we compare the results of the algorithm on a sequence of 21 λ -values. The results in the form of means and standard deviations (in parentheses) are depicted in Table 4 (logistic mixed model) and Table 5 (Poisson mixed model).

Table 4: Simulation results (mean values, standard deviations in parentheses) for logistic mixed models (Section 5 and Appendix C).

Model	rel.time	rel.iter	rel.ll	rel.fix	active Set
L1	0.58	0.63	6×10^{-4}	0.02	0.98
	(0.18)	(0.28)	(3×10^{-4})	(0.01)	(0.04)
L2	0.41	0.61	8×10^{-4}	0.02	0.87
	(0.09)	(0.18)	(5×10^{-4})	(0.01)	(0.07)
H1	0.21	0.67	9×10^{-4}	0.02	0.83
	(0.07)	(0.32)	(7×10^{-4})	(0.01)	(0.09)
H2	0.28	0.77	8×10^{-4}	0.02	0.84
	(0.14)	(0.96)	(6×10^{-4})	(0.01)	(0.08)

We see for both the logistic and the Poisson mixed model that the approximate algorithm requires noteworthy less computing time and outer iterations. The gain in computing time is impressive and often more than 50%. It is apparent that the two procedures yield similar likelihood function values, although the Poisson mixed model has larger differences than the logistic mixed model. We read off from Table 4 that the parameter estimates are very similar and that the active sets coincide well. Table 5 suggests that the active sets and the parameter estimates differ considerably more between the exact and the approximate algorithm. By a closer look, we do see that the differences originate in the fact that for some data sets the approximate algorithm selects more variables, but with very small fixed-effects coefficients. This explains the low values of activeSet. This problem can be effectively addressed by the two-stage procedures presented in Section 4 of the article.

To sum up, the simulations do not only encourage the attractiveness of the approximate algorithm with respect to speed, but also the need for the two-stage procedures.

Appendix C: Low-dimensional logistic mixed model

In the low-dimensional setting, we compare our methods with the unpenalized maximum likelihood (ML) estimate and the Penalized Quasi-Likelihood (PQL, Breslow and Clayton (1993)) estimate. We

Table 5: Simulation results (mean values, standard deviations in parentheses) for Poisson mixed models (Appendix D).

Model	rel.time	rel.iter	rel.ll	rel.fix	active Set
L1	0.10	0.10	46×10^{-4}	0.12	0.96
	(0.02)	(0.02)	(91×10^{-4})	(0.07)	(0.11)
L2	0.06	0.11	27×10^{-4}	0.13	0.88
	(0.01)	0.02	(8×10^{-4})	(0.10)	(0.10)
H1	0.11	0.17	524×10^{-4}	0.33	0.30
	(0.02)	(0.03)	(697×10^{-4})	(0.35)	(0.26)
H2	0.09	0.17	698×10^{-4}	0.38	0.31
	(0.02)	0.04	(951×10^{-4})	(0.38)	(0.29)
H3	0.19	0.92	1296×10^{-4}	0.10	0.05
	(0.07)	(0.39)	(451×10^{-4})	(0.03)	(0.11)

denote them by glmer and glmmPQL, respectively. The comparison begs the question of how to perform variable selection for glmer and glmmPQL. We need some kind of variable selection procedure such that the results remain comparable with our methods. Hence we suggest to reduce iteratively (backward selection) the number of covariates by dropping those whose p-value is greater than 5%. By doing so, we end up with a model where all variables are significant. We denote these methods by p-glmer and p-glmmPQL.

We present the following two examples in the low-dimensional setting:

L₁:
$$N = 40$$
, $n_C = 10$, $n = 400$, $p = 10$, $\theta_1^2 = \theta_2^2 = 1$ and $s_0 = 5$ with $\boldsymbol{\beta}_0 = (0.1, 1, -1, 1, -1, 0, \dots, 0)^T$.
L₂: $N = 40$, $n_C = 10$, $n = 400$, $p = 50$, $\theta_1^2 = \theta_2^2 = 1$ and $s_0 = 5$ with $\boldsymbol{\beta}_0 = (0.1, 1, -1, 1, -1, 0, \dots, 0)^T$.

The results in the form of median and rescaled median absolute deviation (in parentheses) over 100 simulation runs are depicted in Table 6. There, $|S(\hat{\beta})|$ denotes the cardinality of the estimated active set and TP is the number of true positives (selected variables which are in the true active set). SE is the squared error of the fixed-effect coefficients.

To summarize the variable selection results, we see that the thresholded and the iterative procedures have the smallest active sets. Table 6 suggests that the covariance parameter estimates of *glmmlasso* are considerable biased whereas the covariance parameter estimates of the other procedures are very similar. Concerning fixed-effect parameter estimation, the two-stage approaches perform better and do not show striking differences. Since β_1 and β_2 are not subject to penalization (indicated by *), their bias is smaller compared with the penalized coefficients. It can also be observed that the parameter estimates of p-glmmPQL are biased (Jiang, 2007).

Appendix D: Simulation study for the Poisson mixed model

We are going to present some simulations where the conditional response variable follows a Poisson distribution. It is interesting since the behaviour is different from the binary case. Let us look at two low-dimensional and three high-dimensional designs. Beforehand, let us sum up the most relevant findings.

D.1 Summary for the Poisson mixed model

In this subsection, we are going to give an overview over the properties of the Poisson mixed model. We focus on the similarities and differences to the Gaussian (Schelldorfer et al., 2011) as well as the binary case (Section 5 and Appendix C).

- i) Shrinkage of the covariance parameters due to the ℓ_1 -penalization approach is not an issue. This is in contrast to the logistic mixed model and similar to the Gaussian case.
- ii) If we apply the Lasso ignoring the grouping structure within the observations, the recovery of the true active set fails.

Table 6: Simulation results for the logistic mixed models L_1 and L_2 (rescaled median absolute deviations in parentheses). A * means that the corresponding coefficient is not subject to ℓ_1 -penalization in the $GLMMLasso^{LA}$ estimate.

Model	Method	$ S(\hat{\boldsymbol{\beta}}) $	TP	$\hat{ heta}_1^2$	$\hat{ heta}_2^2$	\hat{eta}_1^*	\hat{eta}_2^*	\hat{eta}_3	\hat{eta}_4	\hat{eta}_5	SE
True		5	5	1	1	0.1	1	-1	1	-1	
L_1	oracle	5	5	0.92	0.82	0.09	0.99	-1	0.99	-0.98	0.18
		(0)	(0)	(0.41)	(0.43)	(0.18)	(0.32)	(0.19)	(0.19)	(0.16)	(0.16)
	glmmlasso	6	5	0.65	0.54	0.08	0.82	-0.72	0.68	-0.74	0.4
		(1.48)	(0)	(0.35)	(0.33)	(0.15)	(0.24)	(0.17)	(0.17)	(0.16)	(0.23)
	glmpath	6	5	-	-	0.05	0.51	-0.54	0.53	-0.57	0.88
		(1.48)	(0)	-	-	(0.13)	(0.16)	(0.17)	(0.15)	(0.15)	(0.46)
	hybrid glmmlasso	6	5	0.97	0.83	0.08	1.02	-1.01	0.99	-1	0.28
		(1.48)	(0)	(0.43)	(0.47)	(0.17)	(0.31)	(0.19)	(0.2)	(0.18)	(0.21)
	hybrid glmpath	6	5	0.95	0.81	0.08	1	-1.01	1	-1	0.25
		(1.48)	(0)	(0.43)	(0.49)	(0.18)	(0.31)	(0.19)	(0.19)	(0.17)	(0.2)
	thres glmmlasso	5	5	0.96	0.83	0.08	0.99	-1	0.99	-0.98	0.2
		(0)	(0)	(0.42)	(0.44)	(0.18)	(0.32)	(0.18)	(0.19)	(0.16)	(0.18)
	thres glmpath	5	5	0.92	0.83	0.08	0.99	-1	0.99	-0.98	0.2
		(0)	(0)	(0.41)	(0.44)	(0.18)	(0.32)	(0.19)	(0.19)	(0.16)	(0.18)
	p-glmer	5	5	0.94	0.83	0.08	1	-1.01	0.99	-0.98	0.23
		(0)	(0)	(0.42)	(0.48)	(0.18)	(0.31)	(0.2)	(0.19)	(0.16)	(0.2)
	p- $glmmPQL$	5	5	0.97	0.87	0.08	0.9	-0.94	0.93	-0.92	0.19
		(0)	(0)	(0.42)	(0.4)	(0.17)	(0.27)	(0.19)	(0.18)	(0.14)	(0.16)
L_2	oracle	5	5	0.95	0.8	0.07	0.99	-0.98	0.99	-1.03	0.16
		(0)	(0)	(0.47)	(0.39)	(0.22)	(0.29)	(0.18)	(0.2)	(0.16)	(0.1)
	glmmlasso	6	5	0.47	0.36	0.05	0.71	-0.46	0.47	-0.49	0.99
		(1.48)	(0)	(0.26)	(0.28)	(0.17)	(0.2)	(0.13)	(0.12)	(0.12)	(0.33)
	glmpath	7	5	-	-	0.04	0.36	-0.37	0.39	-0.42	1.6
		(1.48)	(0)	-	-	(0.14)	(0.13)	(0.09)	(0.1)	(0.1)	(0.39)
	hybrid glmmlasso	6	5	0.97	0.82	0.07	0.99	-1	1.03	-1.04	0.32
		(1.48)	(0)	(0.49)	(0.44)	(0.22)	(0.28)	(0.17)	(0.22)	(0.18)	(0.21)
	hybrid glmpath	7	5	0.94	0.81	0.07	1	-0.99	1.03	-1.05	0.37
		(1.48)	(0)	(0.44)	(0.43)	(0.23)	(0.29)	(0.19)	(0.21)	(0.18)	(0.24)
	thres glmmlasso	5	5	0.98	0.83	0.07	0.99	-1	1.04	-1.04	0.26
		(0)	(0)	(0.45)	(0.42)	(0.22)	(0.29)	(0.17)	(0.22)	(0.16)	(0.21)
	thres glmpath	5	5	0.95	0.8	0.07	1	-1	1.04	-1.04	0.22
		(0)	(0)	(0.42)	(0.41)	(0.22)	(0.28)	(0.17)	(0.22)	(0.16)	(0.18)
	p-glmer	5	5	0.98	0.81	0.07	1	-0.99	1.06	-1.03	0.25
		(0)	(0)	(0.46)	(0.43)	(0.23)	(0.27)	(0.19)	(0.21)	(0.16)	(0.22)
	p- $glmmPQL$	5	5	0.97	0.81	0.06	0.91	-0.93	0.94	-0.96	0.19
		(0)	(0)	(0.43)	(0.32)	(0.2)	(0.25)	(0.18)	(0.21)	(0.17)	(0.13)

- iii) For Poisson mixed models, thres glmmlasso performs best whereas in logistic mixed models hybrid glmmlasso is preferable (see Appendix B).
- iv) For the Lasso, we carried out the R function glmpath for a comparison. However, in all our high-dimensional simulation settings, the function breaks down. Hence we employ the R function glmnet for comparisons.
- v) We observe a slow convergence rate (i.e. many outer iterations are required until convergence) in various real data applications. At the same time, convergence problems do occur in glmnet, too. The number of total iterations is often more than 100.

D.2 Low-dimensional Setting

For the Poisson mixed models simulation study, we look at random-intercept designs. This means that only the intercept has a random effect. Particularly, $\theta \in \mathbb{R}$ and $\Sigma_{\theta} = \theta^2 \mathbf{1}_q$, i.e. q = N. We present two examples in the low-dimensional setting.

L₁:
$$N = 20$$
, $n_C = 10$, $n = 200$, $p = 10$, $\theta^2 = 1$ and $s_0 = 5$ with $\boldsymbol{\beta}_0 = (\frac{1}{20}, \frac{1}{2}, -\frac{1}{2}, \frac{1}{2}, -\frac{1}{2}, 0, \dots, 0)^T$.
L₂: $N = 20$, $n_C = 10$, $n = 200$, $p = 50$, $\theta^2 = 1$ and $s_0 = 5$ with $\boldsymbol{\beta}_0 = (\frac{1}{20}, \frac{1}{2}, -\frac{1}{2}, \frac{1}{2}, -\frac{1}{2}, 0, \dots, 0)^T$.

The results over 100 simulation runs are shown in Table 7.

We read off from the table that the thresholded methods pick less variables than the hybrid pro-

Table 7: Simulation results for the Poisson mixed models L_1 and L_2 (median values and MADs in parentheses). A * indicates that the corresponding coefficient is not subject to ℓ_1 -penalization in the GLMMLasso^{LA} estimate.

Model	Method	$ S(\hat{\boldsymbol{\beta}}) $	TP	$\hat{\theta}^2$	$\hat{\beta}_1^*$	\hat{eta}_2	\hat{eta}_3	\hat{eta}_4	\hat{eta}_5	SE
True		5	5	1	0.05	0.5	-0.5	0.5	-0.5	
т.	1	-	_	0.00	0.11	0.5	0.5	0.40	0.40	0.05
L_1	oracle	5	5	0.89	0.11	0.5	-0.5	0.49	-0.49	0.05
	glmmlasso	(0)	$ \begin{array}{c} (0) \\ 5 \end{array} $	$(0.3) \\ 0.88$	(0.27) 0.24	$(0.05) \\ 0.44$	(0.07) -0.43	$(0.06) \\ 0.42$	(0.05) -0.43	(0.041) 0.1
	giiiiiiiasso	(1.48)	(0)	(0.31)	(0.24)	(0.05)	(0.07)	(0.42)	(0.07)	(0.089)
	glmnet	6	5	(0.51)	0.77	0.29	-0.23	0.23	-0.27	0.83
	giiiilet	(1.48)	(0)	_	(0.36)	(0.16)	(0.16)	(0.14)	(0.14)	(0.61)
	hybrid glmmlasso	7	5	0.9	0.11	0.5	-0.51	0.5	-0.49	0.064
	ny orra giiiiiia	(1.48)	(0)	(0.3)	(0.26)	(0.05)	(0.07)	(0.07)	(0.05)	(0.053)
	hybrid glmnet	6	5	0.89	0.17	0.49	-0.49	0.49	-0.48	0.075
	, 0	(1.48)	(0)	(0.31)	(0.29)	(0.06)	(0.08)	(0.08)	(0.07)	(0.075)
	thres glmmlasso	5	5	0.89	0.11	$\stackrel{\cdot}{0.5}^{'}$	-0.5	$0.49^{'}$	-0.5	$0.053^{'}$
		(0)	(0)	(0.3)	(0.26)	(0.05)	(0.07)	(0.06)	(0.05)	(0.043)
	thres glmnet	5	5	0.89	0.17	0.5	-0.49	0.49	-0.48	0.065
		(0)	(0)	(0.31)	(0.29)	(0.06)	(0.08)	(0.08)	(0.06)	(0.068)
	p-glmer	5	5	0.89	0.11	0.5	-0.5	0.49	-0.5	0.055
		(0)	(0)	(0.3)	(0.26)	(0.05)	(0.06)	(0.07)	(0.05)	(0.045)
	p- $glmmPQL$	5	5	0.86	0.14	0.5	-0.5	0.49	-0.49	0.05
		(0)	(0)	(0.28)	(0.25)	(0.05)	(0.06)	(0.06)	(0.05)	(0.047)
L_2	oracle	5	5	0.93	0.06	0.5	-0.49	0.49	-0.49	0.04
		(0)	(0)	(0.38)	(0.25)	(0.06)	(0.05)	(0.04)	(0.07)	(0.041)
	glmmlasso	9	5	0.89	0.26	0.37	-0.33	0.32	-0.35	0.19
		(2.97)	(0)	(0.31)	(0.21)	(0.05)	(0.07)	(0.06)	(0.08)	(0.088)
	glmnet	6	5	-	0.71	0.21	-0.14	0.12	-0.2	0.96
		(2.97)	(0)	-	(0.28)	(0.15)	(0.17)	(0.17)	(0.13)	(0.58)
	hybrid glmmlasso	9	5	0.89	0.06	0.49	-0.47	0.47	-0.48	0.089
		(2.97)	(0)	(0.32)	(0.25)	(0.06)	(0.05)	(0.05)	(0.06)	(0.057)
	hybrid glmnet	6	5	0.85	0.12	0.48	-0.44	0.43	-0.43	0.24
		(2.97)	(0)	(0.33)	(0.26)	(0.1)	(0.13)	(0.13)	(0.13)	(0.28)
	thres glmmlasso	5	5	0.93	0.06	0.5	-0.49	0.5	-0.49	0.063
		(0)	(0)	(0.37)	(0.25)	(0.05)	(0.05)	(0.05)	(0.07)	(0.054)
	thres glmnet	5	5	0.89	0.13	0.48	-0.45	0.45	-0.44	0.21
	n. mlm. on	(1.48)	(0)	(0.35)	(0.27)	(0.09)	(0.14)	(0.13)	(0.14)	(0.26)
	p-glmer	5	5	0.93	0.06	0.51	-0.49	0.49	-0.49	0.048
	m mlmama DOI	(0)	(0)	(0.37)	(0.24)	(0.06)	(0.05)	(0.04)	(0.07)	(0.044)
	p-glmmPQL	5 (0)	5 (0)	0.88	0.1 (0.24)	0.51 (0.06)	-0.49 (0.05)	0.49 (0.05)	-0.49 (0.06)	0.046 (0.043)
		(0)	(0)	(0.35)	(0.24)	(0.00)	(0.05)	(0.05)	(0.00)	(0.045)

cedures. The glmmlasso covariance parameter estimates do not show a dramatic bias here. Estimation accuracy of the fixed-effect parameters is worst for the glmnet based estimators.

D.3 High-dimensional Setting

We examine the following high-dimensional examples:

$$H_1$$
: $N = 40$, $n_C = 10$, $n = 400$, $p = 500$, $\theta^2 = 1$ and $s_0 = 5$ with $\boldsymbol{\beta}_0 = (\frac{1}{20}, \frac{1}{2}, -\frac{1}{2}, \frac{1}{2}, -\frac{1}{2}, 0, \dots, 0)^T$.
 H_2 : $N = 40$, $n_C = 10$, $n = 400$, $p = 1000$, $\theta^2 = 1$ and $s_0 = 5$ with $\boldsymbol{\beta}_0 = (\frac{1}{20}, \frac{1}{2}, -\frac{1}{2}, \frac{1}{2}, -\frac{1}{2}, 0, \dots, 0)^T$.
 H_3 : $N = 30$, $n_C = 10$, $n = 300$, $p = 500$, $\theta^2 = 0.25$ and $s_0 = 5$ with $\boldsymbol{\beta}_0 = (2, \frac{1}{2}, -\frac{1}{2}, \frac{1}{2}, -\frac{1}{2}, 0, \dots, 0)^T$.

The results in the form of median and rescaled median absolute deviation (in parentheses) over 100 simulation runs are shown in Table 8.

Considering parameter estimation accuracy, the Poisson mixed model shows that the variable screening using *glmnet* fails, resulting in large values of SE. Although the median value of TP is large, the mean value (not shown) is below 5. This behaviour is far more obvious than in the logistic mixed model.

Table 8: Simulation results for the Poisson mixed models H_1 , H_2 and H_3 (median values and MADs in parentheses). A * indicates that the corresponding coefficient is not subject to ℓ_1 -penalization in the $GLMMLasso^{LA}$ estimate.

Model	Method	$ S(\hat{\boldsymbol{\beta}}) $	TP	$\hat{\theta}^2$	$\hat{\beta}_1^*$	\hat{eta}_2	\hat{eta}_3	\hat{eta}_4	\hat{eta}_5	SE
True		5	5	1	0.05	0.5	-0.5	0.5	-0.5	
H_1	oracle	5	5	0.94	0.03	0.5	-0.5	0.5	-0.5	0.02
	, ,	(0)	(0)	(0.28)	(0.17)	(0.03)	(0.03)	(0.05)	(0.04)	(0.02)
	glmmlasso	(2.71)	5	0.92	0.26	0.33	-0.31	0.31	-0.33	(0.000)
	glmnet	(3.71)	(0) 5	(0.26)	(0.17)	$(0.04) \\ 0.16$	(0.04) -0.12	$(0.06) \\ 0.13$	(0.05) -0.18	(0.086) 1.1
	gimnet	(2.97)	(0)	-	0.8 (0.26)	(0.13)	(0.12)	(0.13)	(0.12)	(0.56)
	hybrid glmmlasso	(2.97)	5	0.9	0.26)	0.13) 0.47	-0.46	0.13) 0.47	(0.12) -0.47	0.05
	nybrid giiiiiiasso	(3.71)	(0)	(0.27)	(0.16)	(0.04)	(0.05)	(0.04)	(0.04)	(0.038)
	hybrid glmnet	6	5	0.89	0.13	0.47	-0.45	0.46	-0.47	0.082
	ny bira giiiniet	(2.97)	(0)	(0.28)	(0.23)	(0.06)	(0.09)	(0.09)	(0.07)	(0.096)
	thres glmmlasso	6	5	0.93	0.03	0.49	-0.49	0.49	-0.49	0.04
	8	(1.48)	(0)	(0.28)	(0.17)	(0.03)	(0.04)	(0.05)	(0.04)	(0.037)
	thres glmnet	5	5	$0.92^{'}$	$0.12^{'}$	0.48	-0.47	$0.47^{'}$	-0.49	$0.054^{'}$
	Ü	(0)	(0)	(0.28)	(0.22)	(0.05)	(0.09)	(0.09)	(0.06)	(0.07)
H_2	oracle	5	5	0.92	0	0.5	-0.5	0.5	-0.5	0.017
n_2	oracie	(0)	(0)	(0.22)	(0.16)	(0.04)	(0.03)	(0.04)	(0.04)	
	glmmlasso	11	5	0.22)	0.16	0.32	-0.28	0.04)	-0.32	(0.017) 0.23
	giiiiiiasso	(4.45)	(0)	(0.2)	(0.13)	(0.06)	(0.06)	(0.06)	(0.06)	(0.09)
	glmnet	7	5	-	0.76	0.16	-0.09	0.08	-0.14	1.2
	Similer	(7.41)	(0)	_	(0.2)	(0.13)	(0.13)	(0.12)	(0.15)	(0.44)
	hybrid glmmlasso	11	5	0.87	0.02	0.47	-0.47	0.47	-0.47	0.054
	7 8	(4.45)	(0)	(0.21)	(0.16)	(0.06)	(0.04)	(0.05)	(0.05)	(0.038)
	hybrid glmnet	` 7 ´	5	0.85	0.09	$0.45^{'}$	-0.45	$0.42^{'}$	-0.45	0.093
	v	(7.41)	(0)	(0.26)	(0.14)	(0.08)	(0.11)	(0.12)	(0.08)	(0.12)
	thres glmmlasso	6	5	0.89	-0.01	0.49	-0.49	0.49	-0.48	0.041
		(1.48)	(0)	(0.22)	(0.16)	(0.05)	(0.04)	(0.05)	(0.04)	(0.035)
	thres glmnet	5	5	0.89	0.08	0.48	-0.47	0.45	-0.46	0.067
		(1.48)	(0)	(0.24)	(0.14)	(0.08)	(0.12)	(0.1)	(0.08)	(0.09)
True		5	5	0.25	2	0.5	-0.5	0.5	-0.5	
H_3	oracle	5	5	0.25	1.99	0.5	-0.5	0.5	-0.5	0.009
Ö		(0)	(0)	(0.08)	(0.12)	(0.02)	(0.02)	(0.02)	(0.02)	(0.0096)
	glmmlasso	11	5	0.25	2.11	0.41	-0.39	0.4	-0.4	0.057
	O	(2.97)	(0)	(0.08)	(0.11)	(0.02)	(0.03)	(0.03)	(0.03)	(0.028)
	glmnet	10	`5 [´]	-	2.3	0.33	-0.31	0.3	-0.33	$0.25^{'}$
		(5.19)	(0)	-	(0.12)	(0.05)	(0.06)	(0.06)	(0.07)	(0.12)
	hybrid glmmlasso	11	5	0.24	1.99	$0.49^{'}$	-0.48	0.48	-0.48	0.018
		(2.97)	(0)	(0.07)	(0.13)	(0.02)	(0.02)	(0.02)	(0.02)	(0.011)
	hybrid glmnet	10	5	0.23	1.99	0.49	-0.49	0.49	-0.49	0.016
		(5.19)	(0)	(0.08)	(0.12)	(0.02)	(0.02)	(0.02)	(0.02)	(0.012)
	thres glmmlasso	5	5	0.25	1.99	0.5	-0.49	0.5	-0.5	0.011
		(0)	(0)	(0.07)	(0.12)	(0.02)	(0.02)	(0.02)	(0.02)	(0.011)
	thres glmnet	5	5	0.25	1.99	0.5	-0.5	0.5	-0.5	0.0091
		(0)	(0)	(0.07)	(0.12)	(0.02)	(0.02)	(0.02)	(0.02)	(0.0096)

We conclude by noting that the Poisson mixed model clearly shows that it is of paramount importance to perform variable screening using *glmmlasso* and that it can not be carried out by just applying a standard Lasso procedure (and thereby ignoring the grouping structure).