Conditional Inference for Multivariate Generalised Linear Mixed Models

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Abstract
We propose a method for inference in generalised linear mixed models (GLMMs) and several extensions of these models. First, we extend the GLMM by allowing the distribution of the random components to be non-Gaussian, that is, assuming an absolutely continuous distribution with respect to the Lebesgue measure that is symmetric around zero, unimodal and with finite moments up to fourth-order. Second, we allow the conditional distribution to follow a dispersion model instead of exponential dispersion models. Finally, we extend these models to a multivariate framework where multiple responses are combined by imposing a multivariate absolute continuous distribution on the random components representing common clusters of observations in all the marginal models.

Maximum likelihood inference in these models involves evaluating an integral that often cannot be computed in closed form. We suggest an inference method that predicts values of random components and does not involve the integration of conditional likelihood quantities. The multivariate GLMMs that we studied can be constructed with marginal GLMMs of different statistical nature, and at the same time, represent complex dependence structure providing a rather flexible tool for applications.
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1 Introduction

Generalised linear mixed models (GLMMs) form a flexible class of statistical models, which combines the capability to incorporate non-Gaussian distributions and non-linear link functions, inherited from standard generalised linear models, with the power of representing complex dependence structures using random components in the same fashion as classic (Gaussian) mixed models. Therefore, GLMMs appear as a natural tool in many applications (see Demidenko [2004], McCulloch & Searle [2001], Fahrmeir & Tutz [2001] and Agresti [2002]). However, the power of GLMMs comes with a price: the required inference tools are more demanding than standard statistical models. For instance, the likelihood-based inference requires a non-trivial integration of conditional likelihood quantities. Moreover, some of the simplifications of the integration used in the classic Gaussian mixed models (e.g., the result of conditioning a Gaussian distribution on Gaussian random components yields a Gaussian marginal distribution) do not apply in general for GLMMs. For this reason, several inferential tools are discussed in the literature; see Breslow & Clayton (1993), McCulloch & Searle (2001); see also McCulloch (1997) for a comprehensive study comparing several methods ranging from simple numeric (quadrature) integration of the conditional likelihood to several versions of the EM algorithm.

In this paper we present an alternative method of inference for GLMMs, constructed using inference functions, which avoids integrating likelihood quantities while preserving some of the desirable properties of classic likelihood-based methods. Moreover, this new method applies to GLMMs with minimal requirements for the distribution of the random components, which are not necessarily assumed to be normally distributed, as in the standard setup of GLMMs. For instance, we will be able to consider models with heavy-tailed random components as the multivariate t-distribution.

The methods we expose allow us to construct natural extensions to multivariate GLMMs. The main idea is to construct one GLMM describing each response. It is assumed that there is a natural cluster of observations (e.g., individuals or experimental units). Each of those GLMMs contains random components representing those clusters, i.e., taking the same value.
for all the observations belonging to the same cluster. The multivariate GLMM is then constructed by assuming that the distributions of the random components representing the clusters are the marginal distributions of a multivariate distribution (e.g., a multivariate normal distribution or a multivariate t-distribution). Note that the multivariate generalised linear mixed models (MGLMMs), that we obtain in this way, can have marginal models of different nature which might be defined with different distributions and different link functions. In this way, those multivariate models can simultaneously describe responses of varying nature in a way that is not possible do with classic multivariate Gaussian models. Furthermore, since we defined the random components of the marginal GLMMs using minimal distributional assumptions, we will also obtain a MGLMM constructed with a flexible class of multivariate random components. For instance, the multivariate random components can be multivariate normally distributed or regular elliptical contoured distributed.

The paper is structured as follows. In Section 2 we introduce an extension of GLMMs constructed using random components that are not normally distributed, and by extending the family of conditional distributions. We use a simple case, containing random components representing a grouping of the observations (denoted clusters) due to the observational scheme used in the experiment, to present the ideas behind the inference techniques we propose in Section 2.2, and expose the basic asymptotic properties of those techniques in Section 2.3. Section 2.4 extends the inference techniques to the case of models with complex clustering structures. In Section 3 we discuss the inference for multivariate versions of GLMMs. Section 3.1 presents two simulation studies. The appendices A.1, A.2, and A.3 expose some technical details and involved calculations. Appendix A.4 presents a multivariate extension of the classical inference method based on a Laplace approximation for GLMMs.
2 Extended One Dimensional Generalised Linear Mixed Models

This section will study a one-dimensional extension of standard GLMMs defined with random intercepts, and discuss an estimation technique based on conditional inference for those models. The GLMMs that we consider contain random components that are not necessarily Gaussian distributed. Moreover, they allow the conditional distributions to follow a general dispersion model, and therefore, they enlarge the class of standard GLMMs. We extend the models and inferential techniques described here to a multivariate context in Section 3.

2.1 Generalised Linear Mixed Models with Simple Random Components

Consider the situation where we observe the responses of \( n \) individuals or experimental units. Those responses are viewed as realisations of \( n \) random variables taking values in \( \mathcal{Y} \subseteq \mathbb{R} \), which we denote by \( Y_1, \ldots, Y_n \). Here \( \mathcal{Y} \) is typically \( \mathbb{R}, \mathbb{R}^+ \), a compact real interval or \( \mathbb{Z}^+ \) (corresponding to models defined using for example the Normal, Gamma, von Mises or the Poisson distributions). Suppose that each individual belongs to one, and only one, of \( q \) groups of individuals, referred as *clusters*. We assume that there exist \( q \) independent unobservable random variables taking values in \( \mathbb{R} \), say \( B_1, \ldots, B_q \), termed the *random components*, that will be associated to the clusters as described below. Denote the random vector \((B_1, \ldots, B_q)\) by \( B \). According to the model, the responses \( Y_1, \ldots, Y_n \) are conditionally independent given \( B \). Furthermore, for \( i = 1, \ldots, n \) and each \( b \in \mathbb{R}^q \), \( Y_i \) is conditionally distributed according to a dispersion model (see Jorgensen, 1997 and Cordeiro et al., 2021 or equation (2)) given \( B \), with conditional expectation given by

\[
g \left( \mathbb{E}[Y_i|B = b]\right) = x_i^T \beta + z_i^T b, \quad \text{for all } b \in \mathbb{R}^q. \tag{1}
\]

Here \( g \) is a given *link function*, \( x_i \) is a vector of \( k \) explanatory variables associated to the \( i \)th individual and \( \beta \in \Omega \subseteq \mathbb{R}^k \) is a vector of coefficients,
referred as the *fixed effects*. Furthermore, $z_i$ is a $q$-dimensional allocation vector associating the $i$th individual to one of the $q$ clusters. The $j$th entry of the vector $z_i$ takes the value 1 if the $i$th individual belongs to the $j$th cluster and 0 otherwise. Other forms of allocation vectors are possible, but we restrict to the particular form above to simplify the exposition of ideas.

It is convenient to introduce the following nomenclature and notation for the right side of (1). The linear predictor and the conditional mean response for the $i$th individual ($i = 1,\ldots,n$) are defined by $\eta_i = \eta_i(\beta, b) \overset{\text{def}}{=} x_i^T \beta + z_i^T b$ and $\mu_i = \mu_i(\beta, b) \overset{\text{def}}{=} g^{-1}(\eta_i)$, respectively. The parameter space of the conditional means is denoted by $\mathcal{U} \subseteq \mathbb{R}$ and we write $\mu_i \in \mathcal{U}$. Additionally, denote the random vector of observations $(Y_1,\ldots,Y_n)$ by $\mathbf{Y}$, and the vector of observed responses $(y_1,\ldots,y_n)$ by $\mathbf{y}$.

The specification of the extended GLMM that we consider is completed by defining the distribution of the random components as follows. We assume that $B_1,\ldots,B_q$ are independent and identically distributed according to a distribution that is absolutely continuous with respect to the Lebesgue measure on $\mathbb{R}$, symmetric around zero, unimodal, and possessing finite moments up to the fourth-order. Note that the random components have expectation zero due to the symmetry. Denote the density of this distribution by $\varphi(\cdot,\sigma^2)$, where $\sigma^2 \in \mathcal{V} \overset{\text{def}}{=} \mathbb{R}^+$ is a parameter describing the dispersion of the distribution. Here a typical choice would be a normal or a regular absolute continuous one-dimensional elliptically contoured family of distributions and in this case $\sigma^2$ would be the variance parameter.$^1$

Under the model defined above, the conditional distribution of the $i$th observation $Y_i$ given $\mathbf{B}$ (for $i = 1,\ldots,n$), has a density with respect to a dominating measure $\nu$ (defined on the measurable space $(\mathcal{Y},\mathcal{A})$), taking the form of a dispersion model (see Jorgensen, 1997 and Cordeiro et al., 2021).$^1$

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$^1$Here a one-dimensional elliptically contoured family of distributions is a location and scale family of distributions, with location and scale parameters $\mu$ and $\sigma$, for which the characteristic functions $\phi$, satisfy the functional equation $\phi(t) = e^{i\mu t} \psi(-\frac{1}{2}t\sigma^2)$ for all $t \in \mathbb{R}$, for a given function $\psi$. 

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Therefore, the referred density takes the form
\[ f(y_i|B = b; \beta, \lambda) = a(y_i; \lambda) \exp \left\{ -\frac{1}{2\lambda} d \left\{ y_i; g^{-1}(x_i^T \beta + z_i^T b) \right\} \right\} \]
\[ = a(y_i; \lambda) \exp \left\{ -\frac{1}{2\lambda} d (y_i; \mu_i) \right\} , \ \forall \ y_i \in \mathcal{Y}, \ \forall \ b \in \mathbb{R}^q, \]
where $\beta \in \Omega$ and $\lambda \in \Lambda = \mathbb{R}_+$. The function $d : \mathcal{Y} \times \mathcal{U} \to \mathbb{R}_+$ is the unit deviance and, by definition, satisfies that $d(\mu, \mu) = 0$ and $d(y, \mu) > 0$ for all $(y, \mu) \in \mathcal{Y} \times \mathcal{U}$ such that $y \neq \mu$. The function $a : \mathcal{Y} \times \mathbb{R}_+ \to \mathbb{R}_+$ is a given normalising function. We assume that the unit deviance is regular, that is, $d$ is twice continuously differentiable in $\mathcal{Y} \times \mathcal{U}$ and $\partial^2 d(\mu; \mu)/\partial \mu^2 > 0$ for all $\mu \in \mathcal{U}$. The function $V : \mathcal{U} \to \mathbb{R}_+$ given by $V(\mu) = 2/\{\partial^2 d(\mu; \mu)/\partial \mu^2\}$ for all $\mu$ in $\mathcal{U}$ is termed the variance function (Cordeiro et al. 2021). The conditional variance of $Y_i$ given the random components is $V(\mu_i)/\lambda$. The following families of distributions are examples of dispersion models: Normal, Gamma, inverse Gaussian, von Mises, Poisson, and Binomial families.

We formally define the extended GLMM described above as the family
\[ \mathcal{P} = \{ P_{\beta, \lambda, \sigma^2} : \beta \in \Omega, \ \lambda \in \Lambda = \mathbb{R}_+, \ \sigma^2 \in \mathcal{V} = \mathbb{R}_+ \} \]
of probability measures defined on the product measurable space $(\mathcal{Y}^n, \mathcal{A}^n)$ (where $\mathcal{A}^n$ is the related product $\sigma$-algebra) corresponding to the probability measures defining the extended GLMM described above. Let $\nu$ be the product measure induced by $\nu$. The density of the distributions in $\mathcal{P}$, with respect to $\nu$, are given by
\[ p(y; \beta, \lambda, \sigma^2) \overset{\text{def}}{=} \frac{dP_{\beta, \lambda, \sigma^2}(y)}{d\nu} = \int_{\mathbb{R}^q} \prod_{i=1}^n f(y_i|B = b; \beta, \lambda) \prod_{j=1}^q \phi(b_j; \sigma^2) \ db, \]
for all $y \in \mathcal{Y}^n$, $\beta \in \Omega$, $\lambda \in \Lambda$ and $\sigma^2 \in \mathcal{V}$.

We will use the following set of regularity conditions on the generalised linear mixed model $\mathcal{P}$:

(i) The matrices $X$ and $Z$ have full rank (i.e., rank $k$ and $q$, respectively)

(ii) The link function is strictly monotone, invertible and twice continu-
ously differentiable with bounded first order derivative

(iii) The unit deviance, \( d(y, \mu) \), is twice continuous differentiable with respect to \( \mu \)

(iv) The functions \( \frac{\partial}{\partial \beta} d \{ \cdot; g^{-1}(x_i^T \beta + z_i^T b) \} \) and \( \frac{\partial}{\partial b} d \{ \cdot; g^{-1}(x_i^T \beta + z_i^T b) \} \) are dominated by integrable functions (not necessarily the same dominating functions) for each \( \beta \in \mathbb{R}^k \) and \( b \in \mathbb{R}^q \).

These mild regularity conditions turn out to be minimal requirements for the inference theory that we construct.

Let \( y = (y_1, \ldots, y_n) \) be a realisation of the random vector \( Y \overset{\text{def}}{=} (Y_1, \ldots, Y_n) \) of responses. Under the model \( P \), the likelihood function for the parameters \( \beta, \lambda \) and \( \sigma^2 \), based on \( y \), is

\[
L(\beta, \lambda, \sigma^2; y) = p \left( y; \beta, \lambda, \sigma^2 \right).
\]  

(4)

Usually, the integral in the right side of (3) involved in the calculation of the likelihood function in (4), cannot be evaluated in closed form. In Section 2.2, we introduce an inference method that includes predictions of values of the random components, \( B_1, \ldots, B_q \), and avoids the integration. This inferential procedure will be justified using asymptotic arguments in Section 2.3.

We introduce below two families of probability measures related to \( P \), which will be convenient for presenting and discussing the conditional inference for the GLMMs under discussion. First, consider a statistical model, \( \overline{P} \), constructed on \( Y^n \times \mathbb{R}^q \), collecting the joint distributions of the \( n \) responses and the \( q \) random components. This model, called the joint-model, represents the hypothetical situation in which the random components would be observable. We will use the joint-model to introduce and motivate the inferential techniques we propose.

It is convenient to introduce also the following family of probability measures on \((Y^n, A^n)\), obtained by collecting the distributions constructed with the realisable values of the random components \( B_1, \ldots, B_q \), in the following
way

\[
\mathcal{P}^* = \left\{ P_{\beta, b, \lambda}^* : \frac{dP_{\beta, b, \lambda}^*}{dv}(y) = f^*(y; \beta, b, \lambda) \text{ for all } y \in \mathcal{Y}^n, \beta \in \Omega, b \in \mathbb{R}^q, \lambda \in \Lambda \right\}. \quad (5)
\]

The density of the probability measure referred above is given by

\[
f^*(y; \beta, b, \lambda) \overset{\text{def}}{=} \prod_{i=1}^n f(y_i | B = b; \beta, \lambda) \prod_{i=1}^n a(y_i; \lambda) \exp \left\{ -\frac{1}{2\lambda} d[y_i; \mu_i(\beta, b)] \right\},
\]

for all \( y \in \mathcal{Y}^n, \beta \in \Omega, \lambda \in \Lambda \) and \( b \in \mathbb{R}^q \). We call the family \( \mathcal{P}^* \) the conditional model. This family will be used for defining inference functions, and establishing the basic properties of the inference procedures we will propose.

### 2.2 Conditional Inference for Models with a Single Random Component

Under the joint model \( \mathcal{P} \), the log-likelihood function for estimating \( \beta, \lambda \) and \( \sigma^2 \) based on realisations \( y \) and \( b \) of \( Y \) and \( B \), respectively, is

\[
l(\beta, \lambda, \sigma^2; y, b) \overset{\text{def}}{=} \sum_{i=1}^n \log f(y_i | B = b; \beta, \lambda) + \sum_{j=1}^q \log \varphi(b_j; \sigma^2).
\]

From this perspective, \( b \) is a S-sufficient statistic with respect to \( \sigma^2 \) (since the term of the likelihood function that contains \( \sigma^2 \) depends only on \( b \) and not on \( y \)), and S-ancillary with respect to \( \beta \) and \( \lambda \) (since the term of the likelihood function that contains \( \beta \) and \( \lambda \) involves \( b \) only conditionally). See Barndorff-Nielsen (2014, page 50) or Jørgensen & Labouriau (2012, Section 3.2) for formal definitions.

The decomposition of the likelihood function of the joint model \( \mathcal{P} \), defined in (6), motivates that the inference on \( \sigma^2 \) should be performed using the term

\[
\sum_{j=1}^q \log \varphi(b_j; \sigma^2),
\]

corresponding to base the inference on \( \sigma^2 \) on a sufficient statistic. Following
the same line, the inference on \( \beta \) and \( \lambda \) should be performed only using the term

\[
\sum_{i=1}^{n} \log f(y_i | B = b, \beta, \lambda),
\]

which corresponds to perform conditional likelihood-based inference given an ancillary statistic. Therefore, we propose to estimate \( \beta \) and \( \lambda \) by inserting a reasonable prediction of \( b \), say \( \tilde{b} \) as defined below, into (7) and maximising for \( \beta \) and \( \lambda \). We argue in Section 2.3 that the procedure informally defined here yields sensible estimates.

We turn now to the problem of predicting \( b \). Under the joint model \( \mathcal{P} \), it is natural to predict \( b \) by maximising \( l(\beta, \lambda, \sigma^2; y, b) \) given in (6), i.e., by

\[
\hat{b}(\beta, \lambda, \sigma^2; y) = \arg \max_{b_1, \ldots, b_q} \left\{ \sum_{i=1}^{n} \log f(y_i | B = b, \beta, \lambda) + \sum_{j=1}^{q} \log \varphi(b_j; \sigma^2) \right\}.
\]

However, it is convenient, as we will demonstrate in Section 2.3, to use the following approximation to \( \hat{b} \),

\[
\tilde{b}(\beta, \lambda; y) \overset{\text{def}}{=} \Pi_{B_0} \left( \arg \max_{b_1, \ldots, b_q} \sum_{i=1}^{n} \log f(y_i | B = b, \beta, \lambda) \right),
\]

where \( B_0 \overset{\text{def}}{=} \{ b \in \mathbb{R}^q : \frac{1}{q} \sum_{j=1}^{q} b_j = 0 \} \) is the subspace of the vectors in \( \mathbb{R}^q \) with mean zero, and \( \Pi_{B_0} : \mathbb{R}^q \rightarrow B_0 \) is the projection function given by \( \Pi_{B_0}(y) \overset{\text{def}}{=} y - 1/q \sum_{j=1}^{q} y_j \). Note, that \( \tilde{b} \) is an approximation of \( \hat{b} \), because the last term of the right side of (8) is maximised by setting \( b \) equal to zero. The approximation follows from the continuity of the function \( \varphi(\cdot; \sigma^2) \), which has a unique mode at zero, and because \( \tilde{b} \) is in \( B_0 \).

### 2.3 Asymptotic Properties of the Conditional Inference Method

In this section, we formulate the inferential techniques presented in Section 2.2 using the theory of inference functions (Jørgensen & Labouriau (2012)).
We show that the estimated value of $\beta$ and the predicted values of $b$ are asymptotically Gaussian distributed when the variance, $\sigma^2$, of the random component is small.

We consider below the inference functions

$$
\psi^*_\beta : \Omega \times \mathbb{R}^q \times \mathcal{Y} \to \mathbb{R}^k \text{ and } \psi^*_b : \Omega \times \mathbb{R}^q \times \mathcal{Y} \to \mathbb{R}^q,
$$

which are equivalent to the score functions for estimating $\beta$ and $b$, under $P^*$, with $\lambda$ treated as a nuisance parameter. The inference functions $\psi^*_\beta$ and $\psi^*_b$ referred above are defined by

$$
\psi^*_\beta(\beta, b; y) = \sum_{i=1}^{n} \frac{\partial}{\partial \beta} d\left(y_i; g^{-1}(x_i^T \beta + \tilde{z}_i^T b)\right) = \sum_{i=1}^{n} x_i \frac{\partial}{\partial \mu_i} d\left(y_i; \mu_i\right) g'(\mu_i), \quad (10)
$$

$$
\psi^*_b(\beta, b; y) = \sum_{i=1}^{n} \frac{\partial}{\partial b} d\left(y_i; g^{-1}(x_i^T \beta + \tilde{z}_i^T b)\right) = \sum_{i=1}^{n} z_i \frac{\partial}{\partial \mu_i} d\left(y_i; \mu_i\right) g'(\mu_i). \quad (11)
$$

Note that the score functions for estimating $\beta$ and $b$ are given by $\psi^*_\beta$ and $\psi^*_b$ multiplied by $-\frac{1}{2\lambda}$. However, since $\lambda$ is a positive number the solution to the score equations for $\beta$ and $b$ are exactly the roots of $\psi^*_\beta$ and $\psi^*_b$; in this sense they are equivalent. The inference function $\psi^* : \Omega \times \mathbb{R}^q \times \mathcal{Y} \to \mathbb{R}^{k+q}$ given by

$$
\psi^*(\beta, b; y) = \bigg\{ [\psi^*_\beta(\beta, b; y)]^T, [\psi^*_b(\beta, b; y)]^T \bigg\}^T,
$$

will be used for estimating $\beta$ and predicting $b$. We denote the sequences of roots of the inference functions $\psi^*_\beta$ and $\psi^*_b$ by $\{\hat{\beta}_n\}_{n \in \mathbb{N}}$ and $\{\hat{b}_n\}_{n \in \mathbb{N}}$, respectively, obtained when the number of observations, $n$, increases.

According to the classic theory of inference functions (see Jørgensen & Labouriau 2012, Chapter 4), the estimating functions $\psi^*_\beta$ and $\psi^*_b$ yield consistent estimates under $P^*$. Moreover, the estimates of $\beta$ and $b$ are conditionally asymptotically normally distributed (see the details in appendix A.2). However, our primary interest is on estimating $\beta$ under the extended generalised linear mixed model $\mathcal{P}$. For this purpose, we define below the
inference function \( \psi_\beta : \Omega \times \mathcal{Y} \rightarrow \mathbb{R}^k \) given by

\[
\psi_\beta(\beta; y) \overset{\text{def}}{=} \psi^*_\beta(\beta, \hat{b}; y), \quad \text{for all } \beta \in \Omega \text{ and all } y \in \mathcal{Y},
\]

where \( \hat{b} \) is obtained from the joint solution, \((\hat{\beta}, \hat{b})\), of the estimating equation \( \psi^*_\beta(\beta, b; y) = 0 \) and \( \psi^*_b(\beta, b; y) = 0 \). The theorem below shows that, under the assumed mild regularity conditions, the root of \( \psi_\beta \) are consistent and asymptotically Gaussian distributed when the variance of the random components converges to zero.

**Theorem 2.1.** Under the regularity conditions i-iv, the sequences \( \{\hat{\beta}_n\}_{n \in \mathbb{N}} \) and \( \{\hat{b}_n\}_{n \in \mathbb{N}} \) are consistent (in probability) under \( \mathcal{P}^* \). Moreover, \( \{\hat{\beta}_n\}_{n \in \mathbb{N}} \) is consistent (in probability) under \( \mathcal{P} \). Both sequences are asymptotically Gaussian distributed, when \( n \rightarrow \infty \) and \( \sigma^2 \downarrow 0 \).

**Proof.** See Lemma [A.4] for the consistency of \( \{\hat{\beta}_n\}_{n \in \mathbb{N}} \) and \( \{\hat{b}_n\}_{n \in \mathbb{N}} \) under \( \mathcal{P}^* \). See Lemma [A.5] for the consistency in probability of \( \{\hat{\beta}_n\}_{n \in \mathbb{N}} \) under \( \mathcal{P} \) and Theorem [A.7] in Appendix [A.2.4] for the asymptotic normality when the variance of the random components is sufficiently small.

The parametrisation of the family \( \mathcal{P}^* \) defined above is not identifiable. Note, that a natural parametrisation of \( \mathcal{P}^* \) using the triplet \( (\beta, b, \lambda) \in \Omega \times \mathbb{R}^q \times \Lambda \) is not identifiable. Indeed, according to the Lemma [A.1] proved in the appendix [A.1] for any \( i \in \{1, \ldots, n\} \) and any choice of \( \beta, b \) and \( \delta > 0 \) there exists a \( \beta_\delta \in \Omega \) such that \( \eta_i(\beta, b) = \eta_i(\beta_\delta, b - \delta) \). A convenient solution to this issue is to introduce a constraint and require that \( b \) takes values in \( B_0 \) (i.e., the sub-space of \( \mathbb{R}^q \) of vectors with mean zero), which yields an identifiable parametrisation of \( \mathcal{P}^* \). We adopt this parametrisation and re-write here (5) in the form

\[
\mathcal{P}^* = \left\{ P^{*\beta, b^*, \lambda} : \frac{dP^{*\beta, b^*, \lambda}}{d\nu}(y) = f^*(y; \beta^*, b^*, \lambda) \right. \quad \text{for all } y \in \mathcal{Y}, \beta^* \in \Omega^*, b^* \in B_0, \lambda \in \Lambda \left\},
\]

so the mapping from \( \Omega \times B_0 \times \Lambda \) to \( \mathcal{P}^* \) given by \((\beta^*, b^*, \lambda) \mapsto P^{*\beta, b^*, \lambda} \) is a bijection.

The sequences of estimates \( \{\hat{\beta}_n^*\}_{n \in \mathbb{N}} \) and \( \{\hat{b}_n^*\}_{n \in \mathbb{N}} \) obtained as roots to the inference functions defined as above but with the new identifiable parametri-
sation, yields the same maximum likelihood values as a consequence of Lemma A.1 proved in the appendix [A.1]. By the law of large numbers and Lemma A.4, \((\hat{\beta}_n, \hat{b}_n)\) converges to \((\hat{\beta}, \hat{b})\) in probability under \(P_{\beta, b, \lambda}^*\) for \(q\) and \(n\) converging to infinity.

In Section 3.2, we study the distribution of \(\hat{\beta}\) in a simulated example, where we assume that the random components follow a Gaussian distribution.

### 2.4 A Simple Algorithm for Conditional Inference

The following algorithm implements the inference method described above. The algorithm starts by setting the initial values \(\beta^{(0)}\) and \(\lambda^{(0)}\) for the parameters \(\beta\) and \(\lambda\). We used the estimated values of the corresponding parameters of a generalised linear model defined with the same distribution and link function as in the extended GLMM in study, and with the linear predictor given by the fixed effects of the extended GLMM in discussion. The algorithm repeats the following two steps, starting with \(m = 0\), until convergence:

1. Let \(\beta^{(m)}\) and \(\lambda^{(m)}\) be the current estimates of the parameters \(\beta\) and \(\lambda\). Set

   \[
   b^{(m+1)} = \arg \max_{b_1, \ldots, b_q} \sum_{i=1}^{n} \log f(y_i | B = b, \beta^{(m)}, \lambda^{(m)}),
   \]

   and

   \[
   b^{(m+1)}_* = \tilde{b}(\beta^{(m)}, \lambda^{(m)}; y) = \Pi_{B_0} \left( b^{(m+1)} \right),
   \]

   with \(\tilde{b}\) is defined as in (9).

2. Given the latest predicted values of the random components denoted \(b^{(m+1)}_*\), \(\beta^{(m+1)}\) and \(\lambda^{(m+1)}\) are estimated by maximising

   \[
   \prod_{i=1}^{n} f^*(y_i; \beta, b^{(m+1)}_*, \lambda)\]

   with respect to \(\beta\) and \(\lambda\).

After convergence has been obtained, we estimate the variance, finding the
value of $\sigma^2$ that maximises the integral

$$
\int_{B_0} g(\hat{b}; b, \Sigma_{\hat{b}}) \prod_{j=1}^{q} \varphi(b_j; \sigma^2) db,
$$

where $\hat{b}$ denotes the value of $b^{(m+1)}$ in the last round of the algorithm. Here, $g(\cdot; b, \Sigma_{\hat{b}})$ denotes the density of the predicted values from the final iteration, $\hat{b}$, with expectation $b$ and covariance $\Sigma_{\hat{b}}$. In the case where $\sigma^2$ is small enough and $n$ is large enough, this density is close to the multivariate Gaussian density, see Theorem 2.1 for details. In Appendix A.3, calculations of the above integral are given in the case where $g$ and $\varphi$ are densities of Gaussian distributions.

2.5 Conditional Inference for Models with Complex Random Components

This section extends the methods introduced in section 2.3 to a context with complex random components. We first consider non-nested random components, and then we study a scenario where the random components are nested or a combination of the two cases.

When the random components are not nested, the values of the random components are easily predicted using the already described method. To simplify the notation, consider a one dimensional extended GLMM with two vectors of non-nested random components (each corresponding to a clustering of the observations), say $B_1$ and $B_2$ with length $q_1$ and $q_2$, respectively. We assume that $Y_1, \ldots, Y_n$ are conditional independent random variables given $B_1$ and $B_2$, and conditionally distributed according to a dispersion model, with conditional density $f(\cdot | B_1 = b_1, B_2 = b_2, \beta, \lambda)$, where $f$ is defined in (2).

Recall, that values of the random components were predicted using Equation (9), which is equivalent to solving the inference functions in (10) and (11). This equation can easily be adapted to the situation with multiple non-nested random components. To do so, we replace $B_0$ by $\hat{B}_0 \overset{def}{=} \{(b_1, b_2) \in \mathbb{R}^{q_1+q_2} : b_1 \in B_0(\mathbb{R}^{q_1})$ and $b_2 \in B_0(\mathbb{R}^{q_2})\}$ (where $B_0(\mathbb{R}^{q})$ is the space
of vectors of $\mathbb{R}^q$ with mean zero) and define

$$\tilde{b}(\beta, \lambda; y) \overset{\text{def}}{=} \Pi_{B_0} \left[ \arg \max_{(b_1, b_2) \in \mathbb{R}^{q_1+q_2}} \sum_{i=1}^{n} \log f(y_i | B_1 = b_1, B_2 = b_2; \beta, \lambda) \right].$$

We turn now to the case of two nested vectors of random components $B_1$ and $B_2$, where $B_1$ is nested in $B_2$, that is, the clusters corresponding to the entries in $B_2$ groups multiple clusters associated with $B_1$. Therefore, the variation in $B_1$ should be interpreted as the remaining variation not explained by $B_2$. In this case, we estimate the model including only the random component $B_1$. After predicting (temporary) values for $B_1$ denoted by $\bar{b}_1$, we predict the final values of $b_2$ by

$$\hat{b}_2 = (Z_2^T Z_2)^{-1} Z_2^T \bar{b}_1,$$

where $Z_2$ a $q_1 \times q_2$ dimensional matrix with the $(i, j)$'th entry equal to one if the cluster corresponding to the $i$'th entry of $B_1$ is contained in the $j$'th cluster associated with the $j$'th entry of $B_2$, and zero otherwise. Next, the predicted values of $b_1$ is updated to the final values by

$$\hat{b}_1 = \bar{b}_1 - Z_2 \hat{b}_2.$$

These methods can easily be generalised to the multivariate case by using the approach described in Section 3.

### 3 Multivariate Models

In this section, we extend the methods described so far in one dimension to a multivariate context. Consider $d$ response vectors simultaneously observed, each of them following an GLMM described in Section 2. Here the $d$ responses might follow different dispersion models, use different link functions, but the $d$ marginal extended GLMMs must have a common random component with the same clusters for each of the response vectors. The inference method presented in the Sections 2.2 - 2.5 yields predicted values of the random components directly as an additional product of the estimation process.
3.1 Basic Setup

We introduce the following notation required for formally defining the multivariate model we have in mind. Let \( \mathbf{Y} = \{ \mathbf{Y}_1, \ldots, \mathbf{Y}_d \} \) be a \( n \times d \) dimensional response variable matrix, and \( \mathbf{B} = \{ \mathbf{B}(1), \ldots, \mathbf{B}(d) \} = \{ \mathbf{B}_1, \ldots, \mathbf{B}_q \}^T \) a \( q \times d \) dimensional matrix of random components. Each column of \( \mathbf{Y} \) corresponds to \( n \) response variables in a univariate model. We assume, that the rows of \( \mathbf{B} \) are independent and identical distributed according to a multivariate distribution which is absolute continuous with respect to the Lebesgue measure, symmetric around the vector of zeros, unimodal, and with finite moments up to fourth order. We will let \( \Sigma \) denote a covariance matrix of the distribution and \( \varphi(\cdot, \Sigma) \) the density. Often, this distribution will be assumed to be multivariate Gaussian with expectation zero and covariance matrix given by \( \Sigma \).

For \( i = 1, \ldots, n \) and \( j = 1, \ldots, d \), we assume that \( Y_{ij} \) is conditional distributed according to a dispersion model given \( \mathbf{B}(j) = \mathbf{b}(j) \). That is, \( Y_{ij} | \mathbf{B}(j) = \mathbf{b}(j) \sim \mathcal{D}(\mu_{ij}, \lambda_j) \) for \( i = 1, \ldots, n \) and \( j = 1, \ldots, d \), where \( \mathcal{D}(\mu; \lambda) \) denotes the dispersion model distribution with expectation \( \mu \) and dispersion \( \lambda \). The conditional expectation, \( \mu_{ij} \), is connected to the linear predictor, \( \eta_{ij} \), through the known link function denoted \( g_j \), that is, \( g_j(\mu_{ij}) = \eta_{ij} = x_{ij}^T \beta_j + z_i^T \mathbf{b}(j) \), where \( x_{ij} \) and \( z_i \) denote the vector of explanatory variables and a location vector, respectively. Notice, that like in the one dimensional model, \( z_i \) has one entry equal to one and the remaining entries are equal to zero. Thus, \( z_i \) has a one in the entry corresponding to the cluster that the \( i \)th individual belongs to. The conditional density of \( Y_{ij} \) given \( \mathbf{B}(j) \) is denoted by \( f_j \).

We assume, that \( Y_{ij} \) and \( Y_{i'j} \) are conditionally independent given \( \mathbf{B}(j) = \mathbf{b}(j) \) for \( i \neq i' \) (\( i, i' = 1, \ldots, n \)). Moreover, the structure of the model implies that \( Y_{ij} \) and \( Y_{i'j'} \) are conditionally independent given \( \mathbf{B}(j) \) and \( \mathbf{B}(j') \) for all \( i, i' = 1, \ldots, n \) and \( j, j' = 1, \ldots, d \) such that \( j \neq j' \).

3.2 Simulation Studies

In this section, we present results of two simulation studies illustrating basic properties of the proposed estimation procedure. Moreover, we compare
the behaviour of the proposed estimates with two other inference methods: the multivariate Laplace approximation suggested by Breslow & Clayton (1993) (see Appendix A.4 for details) and a Hermite quadrature estimation procedure. Two simulation studies are presented to study the distribution of the estimates when the entries in the covariance matrix are varied, and the bias of the estimated parameters when we increase the numbers of clusters of the random component (and thereby the number of observations). In both simulation studies, we simulate a two dimensional generalised linear mixed model, where \( Y_{ij} \) for \( i = 1, \ldots, n \) and \( j = 1, 2 \) denotes the response variables. We follow the notation introduced above and let \( B_{(1)} \) and \( B_{(2)} \) denote \( q \)-dimensional random vectors representing the random components in the model. We assume that \( Y_{11}, \ldots, Y_{n2} \) are conditionally independent given \( B_{(1)} \) and \( B_{(2)} \). Moreover, we assume that given \( B_{(1)} \) and \( B_{(2)} \), \( Y_{i1} \) and \( Y_{i2} \) are conditionally distributed according to a Gaussian and a Poisson distribution, respectively, with conditional expectations given by

\[
\begin{align*}
E[Y_{i1}|B_{(1)} = b] &= x_{i1}^T \beta + z_{i1}^T b \quad \text{for } i = 1, \ldots, n, \\
E[Y_{i2}|B_{(2)} = b] &= \exp \left( x_{i2}^T \beta + z_{i2}^T b \right) \quad \text{for } i = 1, \ldots, n,
\end{align*}
\]

where \( \beta = (\beta_1, \beta_2) = (1.90, 0.21) \). The Gaussian conditional distribution is assumed to have a variance of 0.5 which is not varied in the simulations.

We assume that \( B^T = (B_{(1)}^T, B_{(2)}^T) \) is Gaussian distributed with expectation zero and covariance structure given by

\[
\begin{align*}
\text{Cov}(B_{(1)}^l, B_{(2)}^l) &= \Sigma \quad \text{for } l = 1, \ldots, q, \\
\text{Cov}(B_{(1)}^l, B_{(2)}^k) &= 0 \quad \text{for } l, k = 1, \ldots, q \text{ such that } l \neq k,
\end{align*}
\]

where \( B_{(j)}^l \) denotes the \( l \)th entry in \( B_{(j)} \) for \( j = 1, 2 \), and

\[
\Sigma = \text{const} \begin{pmatrix} 0.28 & 0.09 \\ 0.09 & 0.12 \end{pmatrix}, \tag{14}
\]
with the constant depending on the simulation study. That is,

\[ \mathbf{B} \sim N_{2q}(0, \Sigma \otimes \mathbf{I}_n), \]

where \( \mathbf{I}_m \) denotes a \( m \)-dimensional identity matrix.

In the first simulation study, we simulate the above described model for three different covariance matrices, corresponding to three different values of the constant in (14). In that way, we can examine the sensitivity in the normality of the estimates to an increase in the variance. Theorem 2.1 states that under some regularity conditions, the estimated values of \( \mathbf{\beta} \) should be Gaussian distributed when the variance of the random components goes to zero. That is, the lower the constant in (14) is, the closer is the distribution of \( \mathbf{\beta} \) to a Gaussian distribution. In this simulation study, we used the following constants: \( c_1 = 1, c_2 = 50 \) and \( c_3 = 100 \). In each of the three simulation studies we simulate 500 datasets and estimate the above described model for each simulation. The results are presented in Figure 1.

In the second simulation study, we fix the covariance matrix of the random components to \( \Sigma \) defined in (14) with the constant set to one. In this study, we vary the lengths of \( \mathbf{B}_{(1)} \) and \( \mathbf{B}_{(2)} \) between the values 10, 50 and 100, whereas the lengths was fixed to 60 in the above described simulation study. For each value of \( q \) (the length of each vector of random components), we simulate the model 500 times and estimate the bias and standard errors of the parameters.
Figure 1: QQ-plot of the theoretical Gaussian quantiles versus the sample quantiles of the estimated values of $\beta_1$ and $\beta_2$ in the described multivariate generalised linear mixed model for different sizes of $\Sigma$. The numbers in the plots are the resulting p-values from Shapiro Wilk tests for normality.
Figure 2: Estimated bias calculated from simulations of the described model for three different lengths of the vectors of random components using three different inference methods. The error bars show the estimated bias plus/minus the estimated standard errors. The Hermite approximation was applied to each univariate marginal model; therefore, there are no estimates for covariances when using this method.
4 Discussion

The inference method introduced in this paper extends the applicability of standard GLMMs in two ways: first, it allows for defining and inferring multivariate GLMMs, provided there exist random components representing clusters of observations defined in the same way in each of the marginal GLMMs; second, it allows to use non-Gaussian distributions for the random components.

Remarkably, the marginal models of the defined MGLMMs can be of different statistical nature and at the same time represent complex dependence structures. Therefore, those models provide a rather flexible tool for applications. For instance, in Pelck & Labouriau (2020) the MGLMM contained marginal GLMMs for binomial and for Poisson distributed responses, which appeared naturally in the process of modelling a system for monitoring the development of roots over time. Moreover, the MGLMM used in Pelck & Labouriau (2020) could be used to detect and represent a first-order Markovian dependence induced by repeated measurements applied at the same experimental units over time (see also Shanmugam et al. (2021) for a similar application on roots development studies). Another example of MGLMMs including marginal GLMMs of different nature can be found in Pelck et al. (2021b), where marginal GLMMs defined with the Gamma, binomial and the compound Poisson families of distributions were used for simultaneously modelling the development of a fungal infection in apples and the concentration of a series of volatile organic compounds, observed along time. In a third study, Pelck et al. (2021a) used MGLMMs to simultaneously describe the students’ marks obtained in different admission exams at the University (Gaussian distributed), and the performance in the course of geometry measured as the number of attempts required to pass the course (a Cox proportional model with discrete time). Those examples illustrate the usefulness of the MGLMMs studied in this paper.

The inference method proposed in this paper does not involve integration of conditional likelihood quantities, which might be advantageous with respect to naive integration based methods, as illustrated in the simulation study presented in Section 3.2. The performance of the new introduced
method is similar to the method introduced by Breslow & Clayton (1993), when we assume the random components to be Gaussian distributed. Indeed, when the random components are Gaussian distributed, the inference functions $\psi^*_g$ and $\psi^*_b$ are similar (but not the same) to the approximate score functions used in Breslow & Clayton (1993), which are based on a Laplace approximation of the likelihood function of the GLMM $P$. In this case, the inference function in (10) is equivalent to the score equation of the fixed effects in Breslow & Clayton (1993), whereas the inference function in (11) differs from the score equation for the random effects by the additive term $\sigma^2 I_q b$, which has expectation zero. We extend the Laplace approximation method proposed by Breslow & Clayton (1993) to a multivariate context in the Appendix A.4.

The GLMMs and MGLMMs described in this paper are constructed using dispersion models instead of exponential dispersion models as usually done in the literature of GLMMs, see Breslow & Clayton (1993) and the literature referred there. We remark that the class of dispersion models defined in Jørgensen (1987), Jørgensen et al. (1996) is much larger than the class of exponential dispersion models; see Cordeiro et al. (2021) and Labouriau (2020) for a list of examples and a discussion of the extension of the class of dispersion models.

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Appendix

A.1 On the identifiability of the family of conditional densities $\mathcal{P}^\ast$

Here, we show that the family of conditional densities given by (5) is not identifiably parametrised by $(\beta, b, \lambda) \in \Omega \times \mathbb{R}^q \times \Lambda$.

Lemma A.1. For any $i \in \{1, \ldots, n\}$ and any choice of $\beta$, $b$ and $\delta > 0$, there exist $\beta_\delta \in \Omega$ such that $\eta_i(\beta, b) = \eta_i(\beta_\delta, b - \delta)$.

Proof. Take arbitrary $i$, $(\beta, b)$ and $\delta > 0$. Note that $z_i^T (b - \delta) = z_i^T b - \delta$ because, by construction, there is one entry of the allocation vector $z_i$ that is equal to one and the other entries vanish. Assume, without loss of generality, that the first entry of the vector $x_i$ is equal to 1 (i.e., the fixed effect of the GLMM contains an intercept) so that $x_i^T \beta = \beta_1 + \tilde{x}_i^T \tilde{\beta}$, where $\tilde{x}_i$ and $\tilde{\beta}$ are the $(k - 1)$-dimensional vectors obtained by eliminating the first entry of $x_i$ and $\beta$, respectively. Taking $\beta_\delta = (\beta_1 + \delta, \beta_2, \ldots, \beta_k)$ we have that

$$\eta_i(\beta, b) = x_i^T \beta + z_i^T b = \beta_1 + \tilde{x}_i^T \tilde{\beta} + z_i^T b = (\beta_1 + \delta) + \tilde{x}_i^T \tilde{\beta} + z_i^T (b - \delta)$$

$$= x_i^T \beta_\delta + z_i^T (b - \delta) = \eta_i(\beta_\delta, b - \delta)$$

The proof follows since $i$, $(\beta, b)$ and $\delta$ were taken arbitrarily. \qed
A.2 Technical Proofs of the Asymptotic Distribution of the Conditional Inference Based Estimates

In this appendix, we present a sequence of lemmas and propositions that will culminate with the proof of the Theorem 2.1 which establishes consistency and joint asymptotic normality of the proposed estimator of $\beta$ and the predictor of $b$ for small values of the variance of the random components.

A.2.1 Regular Inference Functions

We recall the definition of regular inference functions used in this appendix for the easy of the reader (see the details in Jørgensen & Labouriau, 2012, Chapter 4, from which we draw heavily). Consider a parametric family of distributions $\mathcal{P} = \{ P_\theta : \theta \in \Theta \subseteq \mathbb{R}^k \}$ and a $\sigma$-finite measure $\mu$ defined on a given measurable space $(\mathcal{X}, \mathcal{A})$. For each $P_\theta \in \mathcal{P}$, we chose a version of the Radon-Nikodym derivative (with respect to $\mu$), denoted by

$$p(\cdot; \theta) = \frac{dP_\theta}{d\mu} (\cdot).$$

**Definition 1.** A function $\Psi : \mathcal{X} \times \Theta \rightarrow \mathbb{R}^k$ is said to be a regular inference function when the following conditions are satisfied for all $\theta = (\theta_1, \ldots, \theta_k) \in \Theta$ and for $i, j = 1, \ldots, k$.

(i) $E_\theta[\Psi(\theta)] = 0$;

(ii) The partial derivative $\partial \Psi(x; \theta)/\partial \theta_i$ exists for $\mu$-almost every $x \in \mathcal{X}$;

(iii) The order of integration and differentiation may be interchanged as follows:

$$\frac{\partial}{\partial \theta_i} \int_{\mathcal{X}} \Psi(x; \theta)p(x; \theta)d\mu(x) = \int_{\mathcal{X}} \frac{\partial}{\partial \theta_i} [\Psi(x; \theta)p(x; \theta)]d\mu(x);$$

(iv) $E\{\psi_i(\theta)\psi_j(\theta)\} \in \mathbb{R}$ and the $k \times k$ matrix

$$V_{\psi}(\theta) = E\{\Psi(\theta)\Psi^T(\theta)\}$$

is positive definite;
(v) $\mathbb{E}\left\{ \frac{\partial \psi_i}{\partial \theta_i} \frac{\partial \psi_j}{\partial \theta_j} \right\} \in \mathbb{R}$ and the $k \times k$ matrix

$$S_{\psi}(\theta) = \mathbb{E}\{\nabla_{\theta} \Psi(\theta)\}$$

is nonsingular.

Here $\psi_i$ denoted the $i^{th}$ component of the vector function

$$\Psi(\cdot) = (\psi_1(\cdot), \ldots, \psi_k(\cdot))^T,$$

and $\nabla_{\theta}$ denotes the gradient operator relative to the vector $\theta$, defined by

$$\nabla_{\theta} f(\theta) = \frac{\partial f}{\partial \theta^T}(\theta).$$

**A.2.2 Some Key Lemmas**

We denote the sequences of roots of the inference functions $\psi^*_\beta$ and $\psi^*_b$ by $\{\hat{\beta}_n\}_{n \in \mathbb{N}}$ and $\{\hat{b}_n\}_{n \in \mathbb{N}}$ respectively, obtained when the number of observations, $n$, increases. Moreover, define $\theta = (\beta, b)$ and $\hat{\theta}_n = (\hat{\beta}_n, \hat{b}_n)$ (for each $n \in \mathbb{N}$). Recall, that the inference function $\psi^* : \Omega \times \mathbb{R}^q \times \mathcal{Y} \to \mathbb{R}^{k+q}$ for estimating $\theta$ under $\mathcal{P}^*$, is defined by

$$\psi^*(\beta, b) = \left\{ [\psi^*_\beta(\beta, b)]^T, [\psi^*_b(\beta, b)]^T \right\}^T,$$

for all $\beta \in \Omega$ and $b \in \mathbb{R}^q$.

**Lemma A.2.** Under the regularity conditions i-iv, the partial inference functions $\psi^*_\beta$ and $\psi^*_b$ are unbiased, that is,

$$\mathbb{E}_{P^*_{\beta, b, \lambda}} [\psi^*_\beta(\beta, b; \mathcal{Y})] = 0,$$

$$\mathbb{E}_{P^*_{\beta, b, \lambda}} [\psi^*_b(\beta, b; \mathcal{Y})] = 0,$$

for all $\beta \in \Omega$, $b \in \mathbb{R}^q$ and $\lambda \in \Lambda$. Moreover, the partial inference functions $\psi^*_\beta$ and $\psi^*_b$ are regular.

**Proof.** We show that $\psi^*_\beta$ is unbiased since the unbiasedness of $\psi^*_b$ follows from the same arguments. Take arbitrarily $\beta \in \Omega$, $b \in \mathbb{R}^q$ and $\lambda \in \Lambda$. We aim to
show that

\[ 0 = \int_Y \psi_\beta^*(\beta, b; y) f^*(y; \beta, b, \lambda) d\nu(y). \]

The regularity conditions ensure that it is allowed to interchange the order of differentiation and integration in the following:

\[
\int_Y \psi_\beta^*(\beta, b; y) f^*(y; \beta, b, \lambda) d\nu(y) \\
= \sum_{i=1}^n \int_Y \frac{\partial}{\partial \beta} \{d(y_i; g^{-1}(x_i^T \beta + z_i^T b))\} f^*(y_i; \beta, b, \lambda) d\nu(y_i) \\
= -2\lambda \sum_{i=1}^n \int_Y \frac{\partial}{\partial \beta} f^*(y_i; \beta, b, \lambda) d\nu(y_i) \\
= -2\lambda \sum_{i=1}^n \frac{\partial}{\partial \beta} \int_Y f^*(y_i; \beta, b, \lambda) d\nu(y_i) = 0.
\]

The proof follows since \( \beta \in \Omega, b \in \mathbb{R}^q \) and \( \lambda \in \Lambda \) are arbitrarily chosen.

The other regularity conditions for the inference functions follow straightforwardly from the assumed regularity conditions i-iv for the GLMM in play. \( \square \)

We introduce some required notation before presenting the next lemma. Define the sensitivity block matrices

\[
S_{\beta b} = \mathbb{E}[\nabla_b \psi_\beta^*(\beta, b; Y)], \quad S_{b \beta} = \mathbb{E}[\nabla_\beta \psi_b^*(\beta, b; Y)], \\
S_{bb} = \mathbb{E}[\nabla_b \psi_b^*(\beta, b; Y)], \quad S_{\beta \beta} = \mathbb{E}[\nabla_\beta \psi_\beta^*(\beta, b; Y)],
\]

and the variability matrices

\[
V_{\beta b} = \mathbb{E}[\psi_b^*(\beta, b; Y) \psi_\beta^*(\beta, b; Y)^T], \quad V_{b \beta} = \mathbb{E}[\psi_\beta^*(\beta, b; Y) \psi_b^*(\beta, b; Y)^T], \\
V_{bb} = \mathbb{E}[\psi_b^*(\beta, b; Y) \psi_b^*(\beta, b; Y)^T], \quad V_{\beta \beta} = \mathbb{E}[\psi_\beta^*(\beta, b; Y) \psi_\beta^*(\beta, b; Y)^T].
\]

Using these, we define

\[
W = D^{-1} = S_{bb} - S_{\beta b} S_{\beta \beta}^{-1} S_{b \beta}, \quad A = S_{\beta \beta}^{-1} + S_{\beta \beta}^{-1} S_{b \beta} W^{-1} S_{bb} S_{\beta \beta}^{-1}, \\
E = -S_{\beta \beta}^{-1} S_{b \beta} W^{-1}, \quad C = -W^{-1} S_{bb} S_{\beta \beta}^{-1}.
\]

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Lemma A.3. The inverse Godambde information for the inference function \( \psi^* \) is the matrix-valued function \( J_{\psi^*}^{-1} : \Omega \times \mathbb{R}^q \rightarrow \mathbb{R}^{(k+q) \times (k+q)} \) defined by

\[
J_{\psi^*}^{-1} = \begin{bmatrix}
J_{\psi^*\beta}^{-1} & (J_{\psi^*\beta}^{-1})^T \\
J_{\psi^*b}^{-1} & J_{\psi^*b}^{-1}
\end{bmatrix},
\]

with

\[
J_{\psi^*\beta}^{-1} = AV_{\beta\beta}A^T + EV_{\beta b}A^T + AV_{\beta^*\beta}E^T + EV_{b b}E^T,
\]
\[
J_{\psi^*\beta}^{-1} = CV_{\beta\beta}A^T + DV_{\beta b}A^T + CV_{\beta b}E^T + DV_{b b}E^T,
\]
\[
J_{\psi^*b}^{-1} = CV_{\beta b}C^T + DV_{\beta b}E^T + CV_{b b}D^T + DV_{b b}E^T.
\]

for all \( \beta \in \Omega \) and \( b \in \mathbb{R}^q \) using the above introduced notation.

Proof. The result follows from the formulas in Chapter 4 in Jørgensen & Labouriau (2012) and inversion of block matrices.

Lemma A.4. Assume the regularity conditions i-iv. Then, for all \( \beta \in \Omega \), \( b \in \mathbb{R}^q \) and \( \lambda \in \Lambda \), it is true that

\[
\hat{\beta}_n \xrightarrow{n \to \infty} \beta \quad \text{and} \quad \hat{b}_n \xrightarrow{n \to \infty} b.
\]

Moreover,

\[
\sqrt{n}(\hat{\theta}_n - \theta) | B = b \xrightarrow{D} N_{k+q}(0, J_{\psi^*}^{-1}(\beta, b)),
\]

implying that

\[
\sqrt{n}(\hat{\beta}_n - \beta) | B = b \xrightarrow{D} N_{k}(0, J_{\psi^*\beta}^{-1}(\beta, b))
\]

and

\[
\sqrt{n}(\hat{b}_n - b) | B = b \xrightarrow{D} N_{q}(0, J_{\psi^*b}^{-1}(\beta, b)).
\]

Proof. The proof follows from the results in Chapter 4 in Jørgensen & Labouriau (2012), and the fact that \( \psi^*_\beta \) and \( \psi^*_b \) are regular inference functions as a con-
A.2.3 On the asymptotic variance of $\hat{\theta}_n$ under the family $\mathcal{P}$

Lemma A.5. Assume the regularity conditions i-iv. The partial solution $\{\hat{\beta}_n\}_{n \in \mathbb{N}}$ of $\psi^*_\beta$ is also a solution to $\psi_\beta = 0$ defined in \([12]\), and the unconditionally asymptotic covariance matrices (for $n$ converging to infinity and $q$ fixed), denoted $AV$, of $\hat{\beta}_n$ and $\hat{b}_n$ are given by

\[
AV(\hat{\beta}_n) = E[J^{-1}_{\psi^*_\beta}(\beta, B)] + \nabla[\hat{\beta}_n(B)], \tag{15}
\]

\[
AV(\hat{b}_n) = E[J^{-1}_{\psi^*_k}(\beta, B)] + I_q \sigma^2, \tag{16}
\]

with $\hat{\beta}_n(B)$ denoting the estimator of $\beta$ as a function of $B$ for all $n \in \mathbb{N}$, $\beta \in \Omega$ and $B \in \mathbb{R}^q$. Moreover,

\[
\hat{\beta}_n \xrightarrow{P, \lambda, \sigma^2} \beta,
\]

for all $\beta \in \Omega$, $\lambda \in \Lambda$ and $\sigma^2 \in \mathbb{R}^+$. 

Proof. If $\hat{\beta}_n$ is a solution to \([12]\) then it is also a solution to \([10]\) when inserting $\hat{\beta}_n$ and $\hat{b}_n$ for a given $n \in \mathbb{N}$.

Take $\beta \in \Omega$, $\lambda \in \Lambda$ and $\sigma^2 \in \mathbb{R}^+$ arbitrarily. The asymptotic covariance matrices follows from the law of total variance and Lemma A.4, which also implies that for all $\epsilon > 0$

\[
P_{\beta, \lambda, \sigma^2}(|\hat{\beta}_n - \beta| > \epsilon) = \int_{\mathbb{R}^q} P_{\beta, \lambda, \sigma^2}^{*}(|\hat{\beta}_n - \beta| > \epsilon \mid B = b) \prod_{j=1}^{q} \varphi(b_j; \sigma^2) db \xrightarrow{n \to \infty} 0,
\]

since $P_{\beta, \lambda, \sigma^2}^{*}(|\hat{\beta}_n - \beta| > \epsilon \mid B = b) \xrightarrow{n \to \infty} 0$ for all $\epsilon > 0$ and $b \in \mathbb{R}^q$. By the regularity assumptions i-iv, we can interchange the order of limit and integration. The proof follows since $\beta \in \Omega$, $\lambda \in \Lambda$ and $\sigma^2 \in \mathbb{R}^+$ are arbitrarily chosen. 

Often the distribution of the random components can be easily simulated in a computational efficient way (e.g., when the random components are normally or t- distributed). In those cases, the expectations and variances
referred in (15) and (16) can be easily obtained using Monte Carlo methods (this includes simulations of $B$ and calculations of estimates of $\beta$ as a function of the simulated values).

### A.2.4 Proof of the Theorem 2.1

The lemma below provides the calculation of the characteristic function of the asymptotic distribution of the sequence of estimated values of $\hat{\beta}_n$ and $\hat{b}_n$, which will be crucial to prove Theorem 2.1.

**Lemma A.6.** Assume the regularity conditions i-iv. There exist two random vectors $Z_{\beta}$ and $Z_b$ with characteristic functions

\[
E[\exp(it_1^T Z_{\beta})] = E[\exp(-\frac{1}{2}t_1^T J_{\psi_{\beta}}^{-1}(\beta, B)t_1)], \quad \text{for all } t_1 \in \mathbb{R}^k,
\]

\[
E[\exp(it_2^T Z_b)] = E[\exp(-\frac{1}{2}t_2^T J_{\psi_{\beta}}^{-1}(\beta, B)t_2)], \quad \text{for all } t_2 \in \mathbb{R}^q,
\]

respectively, such that

\[
\sqrt{n}(\hat{\beta}_n - \beta) \xrightarrow{D} Z_{\beta} \quad \text{and} \quad \sqrt{n}(\hat{b}_n - b) \xrightarrow{D} Z_b.
\]

**Proof.** By Lemma A.4 we have that

\[
\sqrt{n}(\hat{\beta}_n - \beta) | B = b \xrightarrow{D} N_k((0, J_{\psi_{\beta}}^{-1}(\beta, b))).
\]

Let $Z_{\beta}$ denote a random variable distributed according to the above defined conditional asymptotically Gaussian distribution. By the Portmanteau theorem the above is equivalent to

\[
E\left[h(\sqrt{n}(\hat{\beta}_n - \beta)) | B = b\right] \xrightarrow{n \to \infty} E[h(Z_{\beta}) | B = b]
\]
for all continuous bounded functions $h$. Thus, we have that

$$
\mathbb{E}\left[ h(\sqrt{n}(\hat{\beta}_n - \beta)) \right] = \int_{\mathbb{R}^q} \mathbb{E}\left[ h(\sqrt{n}(\hat{\beta}_n - \beta)) \mid \mathbf{B} = \mathbf{b} \right] \prod_{j=1}^{q} \varphi(b_j; \sigma^2) db \xrightarrow{n \to \infty} \int_{\mathbb{R}^q} \mathbb{E}[h(\mathbf{Z}_\beta) \mid \mathbf{B} = \mathbf{b}] \prod_{j=1}^{q} \varphi(b_j; \sigma^2) db
$$

$$
= \mathbb{E}[h(\mathbf{Z}_\beta)],
$$

since we can interchange the order of limit and integration due to the assumed regularity conditions. Therefore, we conclude that

$$
\sqrt{n}(\hat{\beta}_n - \beta) \xrightarrow{D} \mathbf{Z}_\beta.
$$

The characteristic function of $\mathbf{Z}_\beta$ is given by:

$$
\mathbb{E}[\exp(it_1^T \mathbf{Z}_\beta)] = \mathbb{E}[\mathbb{E}[\exp(it_1^T \mathbf{Z}_\beta) \mid \mathbf{B}]] = \mathbb{E}[\exp(-\frac{1}{2}t_1^T J^{-1}_{\psi}(\beta, \mathbf{B})t_1)], \text{ for all } t_1 \in \mathbb{R}^k.
$$

The proof for $\hat{\mathbf{b}}_n$ follows by similar arguments by changing $\hat{\beta}_n$ to $\hat{\mathbf{b}}_n$, and $\mathbf{Z}_\beta$ to $\mathbf{Z}_b$ (by changing $J^{-1}_{\psi}(\beta, \mathbf{B})$ to $J^{-1}_{\psi}(\beta, \mathbf{B})$) in the above. □

The theorem below corresponds to the second part of theorem 2.1

**Theorem A.7.** Under the regularity conditions i-iv, the sequences $\{\hat{\beta}_n\}_{n \in \mathbb{N}}$ and $\{\hat{\mathbf{b}}_n\}_{n \in \math{N}}$ are asymptotically Gaussian distributed, when $n \to \infty$ and $\sigma^2 \to 0^+$ in the following way

$$
\sqrt{n}(\hat{\beta}_n - \beta) \xrightarrow{D_{n \to \infty}} N_k(0, J^{-1}_{\psi}(\beta, 0)),
$$

and

$$
\sqrt{n}(\hat{\mathbf{b}}_n - \mathbf{b}) \xrightarrow{D_{n \to \infty}} N_q(0, J^{-1}_{\psi}(\beta, 0)).
$$
Proof. Consider the characteristic function of $Z_{\beta}$ found in Lemma A.6

$$\mathbb{E}\left[ \exp(it^T Z_{\beta}) \right] = \mathbb{E}\left[ \exp\left(-\frac{1}{2}t^T J_{\psi_{\beta}^{-1}}^{-1}(\beta, B)t\right) \right], \text{ for all } t \in \mathbb{R}^k.$$  (17)

Using a first order Taylor approximation, we find that

$$\exp\left(-\frac{1}{2}t^T J_{\psi_{\beta}^{-1}}^{-1}(\beta, B)t\right) = \exp\left(-\frac{1}{2} \sum_{i=1}^{k} \sum_{j=1}^{k} t_it_j \{J_{\psi_{\beta}^{-1}}^{-1}(\beta, B)\}_{ij}\right) + \exp\left(-\frac{1}{2} \sum_{i=1}^{k} \sum_{j=1}^{k} t_it_j \{J_{\psi_{\beta}^{-1}}^{-1}(\beta, 0)\}_{ij}\right) \times \exp\left(-\frac{1}{2} B^T \sum_{i=1}^{k} \sum_{j=1}^{k} t_it_j \frac{\partial \{J_{\psi_{\beta}^{-1}}^{-1}\}_{ij}}{\partial b}(\beta, 0)ight) R(B), \text{ for all } t \in \mathbb{R}^k,$$

where $R(\cdot)$ is the remainder term which converges to zero when $B$ converges to zero. Thus, for $\sigma^2$ converging to zero, $B$ converges to the expectation which is zero. This imply, that the remainder term converges to zero. Notice, that the second term has expectation zero since $\mathbb{E}[B] = 0$, so inserting the above in (17) yields

$$\mathbb{E}_{Z_{\beta}}[\exp(it^T Z_{\beta})] = \exp\left(-\frac{1}{2}t^T J_{\psi_{\beta}^{-1}}^{-1}(\beta, 0)t\right) + R(B) \xrightarrow{\sigma^2 \to 0} \exp\left(-\frac{1}{2}t^T J_{\psi_{\beta}^{-1}}^{-1}(\beta, 0)t\right).$$

This proves that the asymptotically distribution of $\{\hat{\beta}_n\}_{n \in \mathbb{N}}$ converges to a Gaussian distribution when $\sigma^2$ converges to zero. The argument for $\{\hat{b}_n\}_{n \in \mathbb{N}}$ is equivalent and follows by changing $\hat{\beta}_n$ to $\hat{b}_n$ and $Z_{\beta}$ to $Z_b$ (changing $J_{\psi_{\beta}^{-1}}^{-1}(\beta, B)$ to $J_{\psi_{b}^{-1}}^{-1}(\beta, B)$) in the above. \qed
A.3 Variance Estimation in Models with Gaussian Random Components

In this section, we calculate the integral in Equation (13) under the assumption that

\[ g(\hat{b}; b, \Sigma) = \sqrt{\frac{1}{2\pi}} |\Sigma_{\hat{b}}|^{-\frac{1}{2}} \exp \left( -\frac{1}{2} (\hat{b} - b)^T \Sigma_{\hat{b}}^{-1} (\hat{b} - b) \right) \]

\[ \varphi(b; \sigma^2) = \left( \frac{2\pi\sigma^2}{2} \right)^{-\frac{q}{2}} \exp \left( -\frac{1}{2\sigma^2} b^2 \right). \]

Plugging into the integral yields

\[
\int_{\mathbb{R}^q} g(\hat{b}; b, \Sigma) \varphi(b; (I_q - \frac{1}{q} E_q)\sigma^2) db
= \int_{\mathbb{R}^q} |2\pi \Sigma_{\hat{b}}|^{-\frac{1}{2}} \exp \left( -\frac{1}{2} (\hat{b} - b)^T \Sigma_{\hat{b}}^{-1} (\hat{b} - b) \right) |2\pi \sigma^2 I_q|^{-\frac{1}{2}} \exp \left( -\frac{1}{2} b^T \frac{1}{\sigma^2} I_q b \right) db
= |2\pi \Sigma_{\hat{b}}|^{-\frac{1}{2}} \left( 2\pi \sigma^2 \right)^{-\frac{q}{2}} \exp \left( -\frac{1}{2} \hat{b}^T \Sigma_{\hat{b}}^{-1} \hat{b} \right) |2\pi \left[ \Sigma_{\hat{b}}^{-1} + \frac{1}{\sigma^2} I_q \right]^{-1}|^{\frac{1}{2}} \exp \left( \frac{1}{2} \hat{b}^T \Sigma_{\hat{b}}^{-1} \left[ \Sigma_{\hat{b}}^{-1} + \frac{1}{\sigma^2} I_q \right]^{-1} \Sigma_{\hat{b}}^{-1} \hat{b} \right).
\]

In the case of multiple random components, we maximise the integral above for each random component. If the random components are nested, we only predict values for the random components with the highest number of clusters and then use least squares to predict values for each random component, see Section 2.5. Therefore, the calculations above are changed by replacing \( \sigma^2 I_q \) with \( \sum_{j=1}^{K} \sigma_{B_j}^2 C_j C_j^T \), where \( B_1, \ldots, B_K \) denotes the \( K \in \mathbb{N} \) nested random components, and \( C_m \) the \( q \times q_m \) dimensional matrix specifying for each level \( l \) (\( l^{th} \) row) which entry of \( B_m \) that enters the \( l \)th entry of \( \hat{b} \). Here \( q_m \) is the dimension of the random vector \( B_m \).

In the multivariate model described in Section 3.1, the above integral can be adapted by letting \( \hat{b}^T = (\hat{b}_{(1)}^T, \ldots, \hat{b}_{(d)}^T) \) (and thus changing the dimension of \( \Sigma_{\hat{b}} \)) and replacing \( \sigma^2 I_q \) with \( \Sigma \otimes I_q \).
A.4 Multivariate Extension of the Laplace Approximation Method

We outline how the Laplace approximation in [Breslow & Clayton (1993)] can be extended to the multivariate model described in Section 3.1, when the random components follow a multivariate Gaussian distribution. This extension follows directly from [Breslow & Clayton (1993)] by redefining some matrices and vectors. We shortly describe how this was done in the simulation study in Section 3.2. The extension given below assumes that the marginal GLMMs are defined with exponential dispersion models (as in Breslow & Clayton (1993)) but this can easily be extended to include general dispersion models.

We assume that $B_1, \ldots, B_q$ are i.i.d according to a $d$-dimensional Gaussian distribution with zero mean and covariance matrix $\Sigma$. Let $B^{(j)}$ denote a vector containing all the $j^{th}$ entries of $B_1, \ldots, B_q$ for $j = 1, \ldots, d$. The above distributional assumptions implies that $\tilde{B}^T = [(B^{(1)})^T, \ldots, (B^{(d)})^T]$ is Gaussian distributed with mean zero and covariance matrix $\Sigma \otimes I_q$, where $I_q$ is the $q \times q$-dimensional identity matrix and $\otimes$ denotes the Kronecker product.

Recall that the $i^{th}$ ($i = 1, \ldots, n_j$) response in the $j^{th}$ ($j = 1, \ldots, d$) marginal model was denoted $y_{ij}$. Define for $j = 1, \ldots, d$, the $n_j \times k_j$-dimensional matrix $X[j] = [x_{1j}, \ldots, x_{nj}]^T$, and likewise the $n_j \times q$ matrix $Z[j] = [z_{1j}, \ldots, z_{nj}]^T$. Based on these definitions, we define for $k = k_1 + \ldots + k_d$ and $n = n_1 + \ldots + n_d$, the $n \times k$-dimensional matrix $X = \text{diag}[X[1], \ldots, X[d]]$ and the $n \times dq$-dimensional matrix $Z = \text{diag}[Z[1], \ldots, Z[d]]$. Moreover, we define for each dimension $j = 1, \ldots, d$, the $n_j \times n_j$-dimensional diagonal glm weight matrix $W[j]$ with diagonal entries $w_{ii}^j = \frac{1}{2\lambda_{ij}v_i} \frac{1}{v_i^2} g''(\mu_i) |g''(\mu_i)|^2$, and the $n \times n$ matrix $W = \text{diag}[W[1], \ldots, W[d]]$.

By redefining the matrices $X$, $Z$, $W$, $D = \Sigma \otimes I_q$ and the vectors $\tilde{B}$ and $y^T = (y_{11}, \ldots, y_{nd})$, we can use the Laplace approximation in [Breslow & Clayton (1993)] to estimate the multivariate model.