

# TOPICS ON GENERALIZED LINEAR MIXED MODELS

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## TOPICS ON GENERALIZED LINEAR MIXED MODELS

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The expectation-maximization algorithm has been advocated recently by a number of authors for fitting generalized linear mixed models. However, the E-step typically involves analytically intractable integrals which have to be approximated. In the first part of this dissertation we suggest two alternative approaches to solve this problem. The first one, MCEM-SR, approximates the integrals by using a Monte Carlo method. In practice, most Monte Carlo methods require prohibitively large sample sizes for convergence. In our approach, we show how randomized spherical-radial integration [Genz and Monahan, 1997] can be adopted to dramatically reduce the computational burden of implementing EM. After a standardizing transformation, a change to polar coordinates results in a double integral consisting of a one dimensional integral on the real line and a multivariate integral on the surface of a unit sphere. Randomized quadratures are used to approximate both of them. An attractive feature of the randomized spherical-radial rule is that its implementation only involves generating from standard probability distributions. Another important feature exploits a partial linearity of GLMM with respect to a random effect vector. Having this linearity in mind we can pick the cubature knots on the sphere each of which belongs to a linear hull of a dimension significantly less than that of the sphere. This leads to a drastic reduction of the computational complexity of the suggested algorithm. In addition, the knots are chosen in a way that increases the polynomial accuracy of the approximation. The advantage of this particular SR approach stems from the fact that the complexity of evaluating the integrand dominates that of generating the Monte Carlo points. The resulting approximation at the E-step

has the form of a fixed effects generalized linear model likelihood and so a standard iteratively reweighted least squares procedure may be utilized for the M-step. The other approach we suggest, EM-LA<sub>2</sub>, is based on higher-order Laplace approximation of the integrals. First, we find a closed form of the standardized cumulants for generalized linear models which are the higher-order terms of the Laplace approximation. Then we incorporate those in the EM algorithm resulting in a fast and efficient procedure. We illustrate both methods by fitting models to two well-known data sets, and compare our results with those of other authors.

In the second part of the dissertation, a double saddlepoint approximation is proposed for the number of contingency tables with counts satisfying certain linear constraints. Computation of the approximation involves fitting a generalized linear model for geometric responses which can be accomplished almost instantaneously using the iterated weighted least squares algorithm. The approximation is far superior to other analytical approximations that have been proposed, and is shown to be highly accurate in a range of examples, including some for which analytical approximations were previously unavailable. A similar approximation based on a logistic regression model is proposed for tables consisting of only zeros and ones. A higher-order adjustment to the basic double saddlepoint further improves the accuracy of the approximation in almost all cases.

## **BIOGRAPHICAL SKETCH**

Vadim Victorovich Zipunnikov was born in Zelenograd, Moscow, Russia on May 30, 1978. He completed Moscow School # 618 in 1995. He then received an M.S. in Mathematics from Moscow State University in 2001 and an M.A. in Economics from New Economic School in 2003. Another significant part of Vadim's education came from his five hour per day commute from Zelenograd to the south of Moscow where both colleges were located. When he is not working on Generalized Linear Mixed Models he enjoys photography and spending time with his friends.

This dissertation is dedicated to my parents, Victor Zipunnikov and Irina Zipunnikova.

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# CHAPTER 1

## INTRODUCTION

### 1.1 Introduction

The class of generalized linear models (GLM), introduced by Nelder and Wedderburn [1972], includes many popular statistical models as special cases, including logistic regression for binary responses, loglinear models for counts, as well as normal theory linear models. McCullagh and Nelder [1989] provide an extensive introduction to the topic. A restriction is that the GLM assumes that the observations are independent of one another, which is not the case, for instance, in longitudinal studies, or if the observations are clustered. Generalized linear mixed models (GLMMs) extend the GLM class by including random effects in their linear predictor. The result is a mixed model containing both fixed effects and random effects. Recent reviews of generalized linear mixed models may be found in Agresti et al. [2000], Hobert [2000], McCulloch and Searle [2001], Demidenko [2004], and Jiang [2006].

The likelihood function for a GLMM involves an integral over the distribution of the random effects. The integral is generally intractable analytically and hence some form of approximation must be used in practice to enable likelihood-based inference. Numerical integration using Gauss quadratures (see, for instance, Abramowitz and Stegun [1965]) is not feasible except for low-dimensional integrals (eg. of dimension three or less). Therefore, other methods must be used. The existing approaches to deal with the problem may be divided in two groups. The first one includes analytical approximations using Taylor expansion of the integrand. Laplace approximation of the likelihood integrals (ML-LA) (Tierney and Kadane [1986]) based on a quadratic approximation of the the log of the integrand gained a certain popularity due to its simplicity. A closely

related technique known as Penalized-Quasi Likelihood (PQL) was developed in Schall [1991], Breslow and Clayton [1993] and Wolfinger and O'Connell [1993] and applies some additional approximation to get a tractable form of the approximated likelihood. Finally, h-likelihood (Lee et al.) jointly estimates both fixed and random effects. A few modifications of h-likelihood have been proposed (Lee et al. and Noh and Lee [2007]). In the simplest case, h-likelihood is equivalent to PQL. All three approaches, ML-LA, PQL, and h-likelihood, deliver a fixed error of approximation which cannot be improved without including higher-order terms of the corresponding Taylor expansion, and in a lot of practical cases result in biased estimators of the parameters (see Breslow and Lin [1995], Lin and Breslow [1996], Shun and McCullagh [1995], Raudenbush et al. [2000], and Noh and Lee [2007]).

In contrast, a second group of methods allows, at least theoretically, to make the approximation error as small as we want. Simulated Maximum Likelihood provides an unbiased estimator of the likelihood by generating a Monte Carlo sample from a selected importance sampler (Geyer and Thompson [1992], Durbin and Koopman [1997]). Markov Chain Monte Carlo methods run a Markov Chain sequence eventually converging to a density of interest (see McCulloch [1994], McCulloch [1997], Booth and Hobert [1999]). Finally, the quasi-Monte Carlo technique transforms the integral into one over a unit cube and then approximates the transformed integral with the so-called quasi-Monte Carlo sample (Kuo et al. [2008]). The Expectation-Maximization (EM) algorithm is another way to compute the maximum likelihood estimator (Dempster et al. [1977]). As with direct likelihood approaches the E-step involves some intractable integrals. All the Monte Carlo methods above can be adapted to construct a MC approximation of the E-step integrals (Wei and Tanner [1990]). In the introductory part of the dissertation, we will review and discuss both analytical and Monte-Carlo methods for likelihood-based inference in the GLMM context.

The first part of the dissertation describes two alternative approximations at the E-step of the EM algorithm. The first one, MCEM-SR, approximates the integrals by using a Monte Carlo method. Monte Carlo approximation for EM algorithm was originally proposed by Wei and Tanner [1990]. This approach, which is known as Monte Carlo EM (MCEM), has been applied in the GLMM context in several recent papers including McCulloch (1994, 1997), Booth and Hobert [1999] and Caffo et al. [2005]. In practice, most of the Monte Carlo methods require prohibitively large sample sizes for convergence. One of the main contributions of this dissertation is the use of randomized spherical-radial (SR) integration rules, developed in a series of papers by Genz and Monahan(1997, 1998, and 1999), at the E-step of the EM algorithm. These rules have been shown to dramatically outperform standard integration rules in many situations, resulting in remarkably accurate approximations even in relatively high dimensional problems. After a standardizing transformation, a change to polar coordinates results in a double integral consisting of a one dimensional integral on the real line and a multivariate integral on the surface of a unit sphere. Randomized quadratures are used to approximate both of them. An attractive feature of the randomized spherical-radial rule is that its implementation only involves generating from standard probability distributions. The implementation of MCEM using SR rules described here is an alternative to their use to directly approximate the likelihood function, as proposed by Clarkson and Zhan [2002]. The issue of why our approach is to be preferred boils down to the pros and cons of EM versus direct maximization. For example, the EM algorithm is known to be very stable in a broad range of problems, and the numerical examples discussed later in this paper appear to substantiate this in the GLMM context. Also, the M-step of EM in the GLMM context is equivalent to fitting a GLM, and can therefore be accomplished using the standard iteratively reweighted least squares (IRLS) algorithm. Another important feature exploited in our approach is a partial linearity of GLMM with respect to

a random effect vector. Having this linearity in mind we pick the cubature knots on the sphere, each of which belongs to a linear hull of a dimension significantly less than that of the sphere. This leads to a drastic reduction of the computational complexity of the suggested algorithm. In addition, the knots are chosen in a way that increases the polynomial accuracy of the approximation. The advantage of this particular SR approach stems from the fact that the complexity of evaluating the integrand dominates that of generating the Monte Carlo points.

The other approach we suggest, EM-LA<sub>2</sub>, is based on higher-order Laplace approximation of the integrals. Our main contribution here is that we find a closed form of the standardized cumulants for generalized linear models which are the higher-order terms of the Laplace approximation. Addressing the bias problem several papers have studied higher-order Laplace approximation for GLMMs. Shun and McCullagh [1995] introduced a modified second-order Laplace approximation with a multiplicative correction term. Shun [1997] considered the second-order Laplace approximation for exchangeable arrays and crossed designs and showed how to reduce the computational burden in this case by ignoring terms with decaying contribution. Laplace 6 approximation was developed in Raudenbush et al. [2000] for nested designs and was implemented in the HLM package (Raudenbush et al. [2004] and Diaz [2007]). However, the correction terms used in Laplace 6 are different from those in the second-order Laplace approximation. The Laplace 6 approximation was later modified and implemented via an EM algorithm, providing a more reliable convergence. However, the details of this particular modification are not available in the literature (see Raudenbush et al. [2004] and Ng et al. [2006] for further discussion). Noh and Lee [2007] considered the second-order Laplace approximation in the context of restricted maximum likelihood for binary data. Neither Shun [1997] nor Noh and Lee [2007] recognized that the crossed sums representing the higher-order terms of the Laplace approximation can be written in simpler forms. This

reduces the complexity of calculating the terms from  $O(q^6)$  to  $O(q^2)$ . Similar simplifications for some selected terms were used in Raudenbush et al. [2000]. However, Noh and Lee [2007] suggested a computational procedure to deal with the calculating the higher-order terms which is redundant and much less efficient than the forms we report. The resulting EM-LA<sub>2</sub> approach is applied to two data sets and compared to the other available methods.

In the second part of the dissertation, we consider the problem of determining the number of contingency tables with a given set of linear constraints. We propose a new analytical approximation built on a higher-order saddlepoint approximation which is accurate, easily computed, and outperforms the previously proposed analytical approximations.

The structure of the dissertation is as follows. In the remainder of this chapter, we review GLM and GLMM theory including estimation techniques based on the approximations mentioned above. In Chapter 2, we develop MCEM-SR and EM-LA<sub>2</sub> methodology, and in Chapter 3, we present our method of counting tables using the double higher-order saddlepoint approximation.

## **1.2 Generalized Linear Model**

In this section we will give a short introduction to Generalized Linear Models. McCullagh and Nelder [1989] provides a comprehensive treatment of the topic.

### 1.2.1 The model

Let us start by introducing *exponential dispersion* distribution family which is an essential building block for defining the GLM class. A random variable  $y$  is said to follow an exponential dispersion distribution if its density or probability mass function has the form

$$f(y; \theta, \phi) = h(y) \exp \left\{ \frac{w}{\phi} [y\theta - b(\theta)] + c(y; \phi) \right\} \quad (1.1)$$

for a nonnegative function  $h(y)$ , functions  $b(\theta)$  and  $c(y; \phi)$ , and constant  $w$ . The scalar parameters  $\theta$  and  $\phi$  are called the *canonical parameter* and the *dispersion parameter* respectively. The set  $\Theta = \{\theta : b(\theta) < \infty\}$  is called the *canonical parameter domain*.

Let  $K_y(s)$  be cumulant generating function of random variable  $y$ , that is  $K_y(s) = \log Ee^{ys}$ . Then, if  $y$  follows the distribution given in (1.1),

$$K_y(s) = \frac{1}{\phi} [b(t\phi + \theta) - b(\theta)], \quad s \in \mathbb{R}$$

and, as a consequence, its derivatives are

$$K_y^{(j)}(s) = \phi^{j-1} b^{(j)}(t\phi + \theta), \quad j = 1, 2, \dots$$

Hence, the  $j$ th cumulant of  $y$  is

$$\kappa_j = \phi^{j-1} b^{(j)}(\theta), \quad \theta \in \text{int}\Theta.$$

In particular, we have  $E(y) = \kappa_1 = b'(\theta)$ , and  $\text{var}(y) = \kappa_2 = \phi b''(\theta)$ . Therefore, the function  $b'(\theta)$  is an increasing function over the canonical domain. The mean parameter  $\mu$  is defined to be equal to  $b'(\theta)$ . Monotonicity of  $b'(\theta)$  guarantees the existence of the inverse function  $(b'(\cdot))^{-1}(\mu)$  which is a function of the mean parameter  $\mu$ . Hence, the variance of  $y$  may be represented as a function of the mean:  $\text{var}(y) = \phi b''[(b')^{-1}(\mu)] = \phi V(\mu)$ . The function  $V(\mu)$  is called the *variance function* of the exponential dispersion family.



We are now ready to define the GLM class. Let  $\{y_i\}_{i=1}^n$ 's be observable response variables coming from exponential dispersion distribution (1.1) with means  $\{\mu_i\}_{i=1}^n$ , and let  $\mathbf{x}_i = (x_{i1}, \dots, x_{ip})^T$  be a vector of explanatory variables associated with the  $i$ th response. Correspondingly, a linear predictor  $\eta_i = \mathbf{x}_i^T \boldsymbol{\beta}$  can be defined for the  $i$ th response, where  $\boldsymbol{\beta}$  is a parameter of interest. We assume the existence of a smooth monotone *link* function  $g(\cdot)$  such that  $g(\mu_i) = \eta_i$ . Therefore, the link function  $g(\mu_i)$  determines how the mean response depends on the explanatory variables  $\mathbf{x}_i$ . An important choice of link function is the *canonical link* defined as

$$g(\mu_i) = (b')^{-1}(\mu_i) \quad (1.2)$$

which is well-defined due to monotonicity of  $b'$  and its inverse.

## 1.2.2 IRLS

For the models considered in this dissertation the dispersion parameter  $\phi$  is a known constant, which without loss of generality we set to be one. In addition, we consider only canonical link models, that is,  $\eta_i = \mathbf{x}_i^T \boldsymbol{\beta} = (b')^{-1}(\mu_i)$ . Under these assumptions, the log-likelihood function for the parameter  $\boldsymbol{\beta}$  is

$$l(\boldsymbol{\beta}; \mathbf{y}) = \sum_{i=1}^n w_i (y_i \mathbf{x}_i^T \boldsymbol{\beta} - b(\mathbf{x}_i^T \boldsymbol{\beta})) + \sum_{i=1}^n c(y_i) + \sum_{i=1}^n \log h(y_i). \quad (1.3)$$

The last two terms in (1.3) do not depend on parameter  $\boldsymbol{\beta}$  and can be ignored. So we define the log-likelihood as

$$l(\boldsymbol{\beta}; \mathbf{y}) = \sum_{i=1}^n w_i (y_i \mathbf{x}_i^T \boldsymbol{\beta} - b(\mathbf{x}_i^T \boldsymbol{\beta})). \quad (1.4)$$

The  $n \times p$  covariate matrix,  $\mathbf{X}$ , with the  $i$ th row equal to  $\mathbf{x}_i^T$ , is assumed to be of full column rank  $p$ . To find the maximum likelihood estimator for  $\boldsymbol{\beta}$  we need to solve the

ML equations

$$\frac{\partial l(\boldsymbol{\beta}; \mathbf{y})}{\partial \boldsymbol{\beta}} = \sum_{i=1}^n w_i (y_i - b'(\mathbf{x}_i^T \boldsymbol{\beta})) \mathbf{x}_i = 0. \quad (1.5)$$

which are nonlinear with respect to parameter  $\boldsymbol{\beta}$  and can be solved by using Newton-Raphson (NR) algorithm. In NR, we begin with a reasonable starting value  $\boldsymbol{\beta}^{(0)}$  and calculate updates as

$$\boldsymbol{\beta}^{(k+1)} = \boldsymbol{\beta}^{(k)} - \left[ \frac{\partial^2 l(\boldsymbol{\beta}^{(k)}; \mathbf{y})}{\partial \boldsymbol{\beta} \partial \boldsymbol{\beta}^T} \right]^{-1} \frac{\partial l(\boldsymbol{\beta}^{(k)}; \mathbf{y})}{\partial \boldsymbol{\beta}} \quad (1.6)$$

The convergence is declared at step  $k + 1$  when  $|\boldsymbol{\beta}^{(k+1)} - \boldsymbol{\beta}^{(k)}| < \varepsilon$  where  $\varepsilon$  is a small predefined value or when the change in the log-likelihood (1.4) is negligible.

The second derivative of (1.4) is

$$\frac{\partial^2 l(\boldsymbol{\beta}; \mathbf{y})}{\partial \boldsymbol{\beta} \partial \boldsymbol{\beta}^T} = - \sum_{i=1}^n w_i b''(\mathbf{x}_i^T \boldsymbol{\beta}) \mathbf{x}_i \mathbf{x}_i^T = -\mathbf{X}^T \mathbf{W} \mathbf{X}, \quad (1.7)$$

where matrix  $\mathbf{W}$  is a  $n \times n$  diagonal matrix with  $w_i b''(\mathbf{x}_i^T \boldsymbol{\beta})$  on the main diagonal.

Combining (1.5) and (1.7) in (1.6) we get so-called *Iteratively Reweighed Least Squares* (IRLS) algorithm

$$\mathbf{X}^T \mathbf{W}^{(k)} \mathbf{X} \boldsymbol{\beta}^{(k+1)} = \mathbf{X}^T \mathbf{W}^{(k)} \mathbf{z}^{(k)}, \quad (1.8)$$

where the vector of *working responses*,  $\mathbf{z}^{(k)}$ , has  $i$ th component

$$z_i^{(k)} = g(\mu_i^{(k)}) + g'(\mu_i^{(k)})(y_i - \mu_i^{(k)}). \quad (1.9)$$

The maximum likelihood estimator  $\hat{\boldsymbol{\beta}}$  is asymptotical normal

$$(n \mathbf{X}^T \mathbf{W} \mathbf{X})^{1/2} (\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}) \rightarrow N_p(0, \mathbf{I}_p), \quad \text{as } n \rightarrow \infty. \quad (1.10)$$

The result (1.10) is used for constructing Wald tests and approximate confidence sets.

### 1.2.3 Saddlepoint approximation for GLM

Now we will show how the saddlepoint density for the sufficient statistic of a GLM can be constructed. The results of this section will be used in Chapter 3.

Let  $\mathbf{u} = (u_1, \dots, u_q)^T$  denote a nondegenerate  $q$ -dimensional random variable with moment generating function of  $\mathbf{u}$  given by

$$M(\mathbf{s}) = Ee^{\mathbf{u}^T \mathbf{s}}, \quad \mathbf{s} \in \mathbb{R}^q$$

and cumulant generating function (CGF)

$$K(\mathbf{s}) = \log M(\mathbf{s}), \quad \mathbf{s} \in \mathbb{R}^q.$$

The saddlepoint density approximation for  $\mathbf{u}$  is defined as

$$\hat{f}(\mathbf{u}) = \frac{e^{K(\hat{\mathbf{s}}) - \hat{\mathbf{s}}^T \mathbf{u}}}{(2\pi)^{q/2} \mathbf{det}[K''(\hat{\mathbf{s}})]}, \quad \mathbf{u} \in \mathbb{D} \quad (1.11)$$

where saddlepoint  $\hat{\mathbf{s}}$  is the unique solution to the  $q$ -dimensional saddlepoint equation

$$K'(\hat{\mathbf{s}}) = \mathbf{u}. \quad (1.12)$$

The asymptotic properties of the saddlepoint approximation are usually derived by considering the saddlepoint approximation for the mean of an i.i.d sample. Let  $\bar{\mathbf{u}}$  be the mean of  $n$  i.i.d. random variables with the CGF  $K(\mathbf{s})$ . Then the saddlepoint density approximation for  $\bar{\mathbf{u}}$  is

$$\hat{f}_{\bar{\mathbf{u}}}(\mathbf{u}) = \frac{n^{q/2} e^{nK(\hat{\mathbf{s}}) - n\hat{\mathbf{s}}^T \mathbf{u}}}{(2\pi)^{q/2} \mathbf{det}[K''(\hat{\mathbf{s}})]}, \quad \mathbf{u} \in \mathbb{D} \quad (1.13)$$

and the saddlepoint  $\hat{\mathbf{s}}$  is the unique solution to  $K'(\hat{\mathbf{s}}) = \mathbf{u}$ . Approximation (1.13) has asymptotic order  $O(n^{-1})$ , that is,

$$f(\mathbf{u}) = \hat{f}_{\bar{\mathbf{u}}}(\mathbf{u})(1 + O(n^{-1})). \quad (1.14)$$

The first order term,  $O(n^{-1})$ , will be discussed Chapter 3 where we will study a higher-order correction to (1.14).

From (1.4) it immediately follows that  $\mathbf{t} = \sum_{i=1}^n w_i y_i \mathbf{x}_i^T$  is the sufficient statistic for parameter  $\beta$  with CGF given by

$$K(\mathbf{s}) = \sum_{i=1}^n w_i b(\mathbf{x}_i^T \mathbf{s}), \quad \mathbf{s} \in \mathbb{R}^q. \quad (1.15)$$

Applying (1.11) we obtain the saddlepoint density for the sufficient statistic  $\mathbf{t}$ ,

$$\hat{f}(\mathbf{t}) = \frac{\exp\{\sum_{i=1}^n w_i [b(\mathbf{x}_i^T \hat{\mathbf{s}}) - y_i \mathbf{x}_i^T \hat{\mathbf{s}}]\}}{(2\pi)^{q/2} \mathbf{det}[\sum_{i=1}^n w_i b''(\mathbf{x}_i^T \hat{\mathbf{s}}) \mathbf{x}_i \mathbf{x}_i^T]}, \quad \mathbf{t} \in \mathbb{D}. \quad (1.16)$$

where the saddlepoint,  $\hat{\mathbf{s}}$ , is a unique solution of the saddlepoint equation

$$\sum_{i=1}^n w_i b'(\mathbf{x}_i^T \hat{\mathbf{s}}) = \mathbf{t}. \quad (1.17)$$

Comparing (1.17) with (1.5) we see that the saddlepoint is just the maximum likelihood estimator of parameter  $\beta$ . In addition, the derivatives of the CGF (1.15) are given by

$$K^{(k)}(\mathbf{s}) = -l^{(k)}(\mathbf{s}), \quad \text{for any } k \geq 2. \quad (1.18)$$

where the equality above means the equality of the corresponding partial derivatives of  $K(\mathbf{s})$  and  $-l(\mathbf{s})$ . In particular,  $\hat{K}''$  is equal to the estimated information matrix  $\hat{\mathbf{I}}_{\beta\beta} = \mathbf{X}^T \hat{\mathbf{W}} \mathbf{X}$ .

### 1.3 Generalized Linear Mixed Models

Generalized linear mixed models (GLMMs) extend the GLM class by including random effects in their linear predictor. This section provides a review of GLMMs as well as the most popular estimation techniques. More details on generalized linear mixed models may be found in the recent textbooks by McCulloch and Searle [2001], Demidenko [2004], and Jiang [2006].

### 1.3.1 The model

A generic description of a GLMM is as follows. Let  $\mathbf{y}_i = (y_{i1}, \dots, y_{in_i})^T$ ,  $i = 1, \dots, n$ , be independent random response vectors. Let  $\mathbf{x}_{ij}$  and  $\mathbf{z}_{ij}$  denote known  $p$ - and  $q$ -dimensional covariate vectors associated with the  $j$ th component of  $\mathbf{y}_i$ . Dependence between the components of the  $\mathbf{y}_i$ 's is induced by unobservable  $q$ -dimensional random effects vectors,

$$\mathbf{u}_i^\Sigma = (u_{i1}^\Sigma, \dots, u_{iq}^\Sigma)^T \sim \text{i.i.d. } N_q(\mathbf{0}, \Sigma), \quad i = 1, \dots, n,$$

where  $\Sigma$  is assumed to be positive definite. Conditionally on the random effect  $\mathbf{u}_i^\Sigma$ , the univariate components,  $y_{ij}$ ,  $j = 1, \dots, n_i$  are independent with means,  $\mu_{ij} = E(y_{ij} | \mathbf{u}_i^\Sigma)$ , satisfying

$$g(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \mathbf{z}_{ij}^T \mathbf{u}_i^\Sigma, \quad (1.19)$$

where  $\boldsymbol{\beta}$  is a  $p$ -dimensional parameter and  $g(\cdot)$  is a link function. Since  $\Sigma$  is positive definite there exists a unique  $q \times q$  lower-triangular matrix  $\mathbf{D}$  with positive diagonal entries such that  $\Sigma = \mathbf{D}\mathbf{D}^T$ , and hence

$$\mathbf{u}_i^\Sigma \stackrel{d}{=} \mathbf{D}\mathbf{u}_i, \quad \text{where } \mathbf{u}_i \sim \text{i.i.d. } N_q(0, \mathbf{I}_q), \quad i = 1, \dots, n.$$

Therefore, without loss of generality, we may consider the distributionally equivalent form,

$$g(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \mathbf{z}_{ij}^T \mathbf{D}\mathbf{u}_i \quad (1.20)$$

in place of (1.19) [Demidenko, 2004, page 411]. In this work, we only consider situations when matrix  $\mathbf{D}$  can be characterized by a few non-zero parameters. Let  $\boldsymbol{\sigma}$  be a  $q^*$ -dimensional vector containing these unique non-zero parameters. Then, it is easy to see that there exists a  $q^* \times q$  matrix  $\mathbf{P}(\mathbf{z}_{ij})$  such that

$$\mathbf{z}_{ij}^T \mathbf{D} = \boldsymbol{\sigma}^T \mathbf{P}(\mathbf{z}_{ij}).$$

Entries of matrix  $\mathbf{P}(\mathbf{z}_{ij})$  are formed by some sums of components  $\mathbf{z}_{ij}$  corresponding to the parameter  $\boldsymbol{\sigma}$  to satisfy to the equality above. Let us denote

$$\boldsymbol{\xi}_{ij} = \mathbf{P}(\mathbf{z}_{ij})\mathbf{u}_i. \quad (1.21)$$

It will sometimes be more convenient to use an alternative representation of (1.21) given by

$$\boldsymbol{\xi}_{ij} = \mathbf{G}^T \text{vech}(\mathbf{z}_{ij}\mathbf{u}_i^T) \quad (1.22)$$

for a  $q(q+1)/2 \times q^*$  matrix  $\mathbf{G}$  of rank  $q^*$  (for more detail see Appendix). Then (1.20) can be rewritten as

$$g(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \boldsymbol{\xi}_{ij}^T \boldsymbol{\sigma}. \quad (1.23)$$

A shorter form of (1.23) is given by

$$g(\mu_{ij}) = \tilde{\mathbf{x}}_{ij}^T \boldsymbol{\psi},$$

where  $\tilde{\mathbf{x}}_{ij} = (\mathbf{x}_{ij}^T, \boldsymbol{\xi}_{ij}^T)^T$  and  $\boldsymbol{\psi} = (\boldsymbol{\beta}^T, \boldsymbol{\sigma}^T)^T$  is a  $(p + q^*)$ -dimensional parameter of interest.

Specification of a GLMM is completed by describing variability in the response,  $y_{ij}$ , about its conditional mean,  $\mu_{ij}$ , using an exponential model of the form

$$f(y_{ij}|\mu_{ij}) = \exp\{w_{ij}[\theta_{ij}y_{ij} - b(\theta_{ij})] + c(y_{ij})\},$$

for some function  $c(\cdot)$ , canonical parameter  $\theta_{ij} = (b')^{-1}(\mu_{ij})$ , and known weights  $w_{ij}$ .

The observable likelihood function for the parameter  $\boldsymbol{\psi}$  is therefore

$$L(\boldsymbol{\psi}; \mathbf{y}) = \int_{\mathbb{R}^q} f(\mathbf{y}|\mathbf{u}; \boldsymbol{\psi}) \phi(\mathbf{u}, \mathbf{I}_{nq}) d\mathbf{u}, \quad (1.24)$$

where  $\mathbf{y} = (\mathbf{y}_1^T, \dots, \mathbf{y}_n^T)^T$  and  $\mathbf{u} = (\mathbf{u}_1^T, \dots, \mathbf{u}_n^T)^T$ ,  $\phi(\mathbf{u}, \mathbf{I}_{nq}) = \prod_{i=1}^n \prod_{r=1}^q \phi(u_{ir})$ ,

where  $\phi(\cdot)$  is the standard normal density, and

$$f(\mathbf{y}|\mathbf{u}; \boldsymbol{\psi}) = \prod_{i=1}^n f(\mathbf{y}_i|\mathbf{u}_i; \boldsymbol{\psi}) = \prod_{i=1}^n \prod_{j=1}^{n_i} \exp\{w_{ij}[\theta_{ij}y_{ij} - b(\theta_{ij})] + c(y_{ij})\}$$

The log-likelihood is therefore

$$l(\boldsymbol{\psi}; \mathbf{y}) = \sum_{i=1}^n \log \int_{\mathbb{R}^q} f(\mathbf{y}_i | \mathbf{u}_i; \boldsymbol{\psi}) \phi(\mathbf{u}_i, \mathbf{I}_q) d\mathbf{u}_i = \sum_{i=1}^n \log \mathfrak{G}_i, \quad (1.25)$$

with

$$\mathfrak{G}_i = \int_{\mathbb{R}^q} f(\mathbf{y}_i | \mathbf{u}_i; \boldsymbol{\psi}) \phi(\mathbf{u}_i, \mathbf{I}_q) d\mathbf{u}_i, \quad i = 1, \dots, n. \quad (1.26)$$

Integrals (1.26) in most practical cases cannot be evaluated explicitly. Therefore, the maximization of (1.24) cannot be accomplished without an approximation of the integral.

### 1.3.2 Example: Minnesota health plan data

Waller and Zelterman [1997] reported data from longitudinal records on 121 senior citizens enrolled in a health plan in Minnesota. The data consist of the number of times each subject visited or called the medical clinic in each of four 6-month periods. Let  $y_{ikl}$  denote the count for subject  $i$ , event  $k$  (visit or call), and period  $l$ . It is natural to consider subject as a random factor, but event and period as fixed. Hence we consider a Poisson loglinear model with  $y_{ikl} | \mathbf{u}_i^\Sigma \sim \text{Poisson}(\mu_{ikl})$ , and

$$\log \mu_{ikl} = a_0 + a_k + b_l + c_{kl} + \gamma_i + v_{ik} + \omega_{il}, \quad k = 1, 2, \text{ and } l = 1, 2, 3, 4, \quad (1.27)$$

where  $a_0$  is an intercept,  $a_k$  is the fixed effect of event  $k$ ,  $b_l$  is the fixed effect of period  $l$ ,  $c_{kl}$  is fixed event  $\times$  period interaction,  $\gamma_i$  is a random effect associated with subject  $i$ ,  $v_{ik}$  is a random subject  $\times$  event interaction, and  $\omega_{il}$  is a random subject  $\times$  period interaction.

The model therefore involves a 7-dimensional random effect

$$\mathbf{u}_i^\Sigma = (\gamma_i, v_{i1}, v_{i2}, \omega_{i1}, \omega_{i2}, \omega_{i3}, \omega_{i4}), \quad i = 1, \dots, 121,$$

associated with the subject  $i$ . We suppose that

$$\mathbf{u}_i^\Sigma \sim \text{i.i.d. } N_7(\mathbf{0}, \boldsymbol{\Sigma}), \quad i = 1, \dots, 121$$

where

$$\boldsymbol{\Sigma} = \begin{pmatrix} \sigma_\gamma^2 & 0 & 0 \\ 0 & \sigma_v^2 \mathbf{I}_2 & 0 \\ 0 & 0 & \sigma_\omega^2 \mathbf{I}_4 \end{pmatrix}$$

We achieve identifiability by setting  $a_2 = b_4 = c_{14} = c_{21} = c_{22} = c_{23} = c_{24} = 0$ . The fixed effects parameter in (1.23) is then

$$\boldsymbol{\beta} = (a_0, a_1, b_1, b_2, b_3, c_{11}, c_{12}, c_{13}).$$

To eliminate the double index  $kl$ , and express the model in the form in (1.23), we consider a new index  $j = 4(k - 1) + l$ . Accordingly,  $(y_{i1}, \dots, y_{i4}, y_{i5}, \dots, y_{i8}) = (y_{i11}, \dots, y_{i14}, y_{i21}, \dots, y_{i24})$  and  $(\mu_{i1}, \dots, \mu_{i4}, \mu_{i5}, \dots, \mu_{i8}) = (\mu_{i11}, \dots, \mu_{i24})$ , for each  $i = 1, \dots, 121$ . In addition, we introduce

$$\mathbf{x}_{ij} = (1, I_{\{1 \leq j \leq 4\}}, I_{\{j=1 \text{ or } 5\}}, I_{\{j=2 \text{ or } 6\}}, I_{\{j=3 \text{ or } 7\}}, I_{\{j=1\}}, I_{\{j=2\}}, I_{\{j=3\}})^T$$

and

$$\mathbf{z}_{ij} = (1, I_{\{1 \leq j \leq 4\}}, I_{\{5 \leq j \leq 8\}}, I_{\{j=1 \text{ or } 5\}}, I_{\{j=2 \text{ or } 6\}}, I_{\{j=3 \text{ or } 7\}}, I_{\{j=4 \text{ or } 8\}})^T$$

where  $I_{\{A\}}$  is the indicator of event  $A$ . With these definitions matrix  $\mathbf{P}(\mathbf{z}_{ij})$  from (1.21)

is equal to

$$\begin{pmatrix} z_{ij1} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & z_{ij2} & z_{ij3} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & z_{ij4} & z_{ij5} & z_{ij6} & z_{ij7} \end{pmatrix}_{3 \times 7}$$

and (1.23) becomes

$$g(\mu_{ij}) = \log(\mu_{ij}) = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \boldsymbol{\xi}_{ij}^T \boldsymbol{\sigma} = \tilde{\mathbf{x}}_{ij}^T \boldsymbol{\psi}$$

where  $\boldsymbol{\sigma} = (\sigma_\gamma, \sigma_v, \sigma_\omega)^T$ ,  $\boldsymbol{\xi}_{ij}^T = (z_{ij1}u_{i1}, z_{ij2}u_{i2} + z_{ij3}u_{i3}, z_{ij4}u_{i4} + z_{ij5}u_{i5} + z_{ij6}u_{i6} + z_{ij7}u_{i7})$ , and  $\mathbf{u}_i \sim \text{i.i.d. } N_7(0, \mathbf{I}_7)$ .



The observable likelihood for the model is

$$L(\boldsymbol{\psi}; \mathbf{y}) = \prod_{i=1}^{121} \int_{\mathbb{R}^7} f(\mathbf{y}_i | \mathbf{u}_i; \boldsymbol{\psi}) \phi(\mathbf{u}_i, \mathbf{I}_7) d\mathbf{u}_i,$$

where the  $i$ th integral in the product is equal to

$$\left(\frac{1}{2\pi}\right)^{7/2} \left(\prod_{j=1}^8 \frac{1}{y_{ij}!}\right) \int_{\mathbb{R}^7} \exp\left(-\sum_{j=1}^8 \exp\{\tilde{\mathbf{x}}_{ij}^T \boldsymbol{\psi}\} + \sum_{j=1}^8 y_{ij} \tilde{\mathbf{x}}_{ij}^T \boldsymbol{\psi} - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i\right) d\mathbf{u}_i,$$

and cannot be evaluated analytically.

Any multi-index model can be reduced to the form (1.24), in a similar manner, by appropriate re-indexing of variables.

In the following subsections we describe a few common methods of approximating likelihood (1.24).

### 1.3.3 Laplace approximation

We will start with Laplace approximation of the GLMM likelihood. Suppose the function  $h(\mathbf{u})$  is a smooth enough function over  $\mathbb{R}^q$  and we want to approximate the integral

$$\mathbf{I}(h) = \int_{\mathbb{R}^q} e^{-mh(\mathbf{u})} d\mathbf{u}. \quad (1.28)$$

If  $h(\mathbf{u})$  has a global minimum at  $\hat{\mathbf{u}}$  then

$$\hat{\mathbf{I}}_{LA}(h) = \frac{(2\pi)^{q/2} e^{-mh(\hat{\mathbf{u}})}}{\sqrt{\det[mh''(\hat{\mathbf{u}})]}} \quad (1.29)$$

is the Laplace approximation of  $\mathbf{I}(h)$  and  $\mathbf{I}(h) = \hat{\mathbf{I}}_{LA}(h)(1 + O(m^{-1}))$  as  $m \rightarrow \infty$  (see, for instance, Butler [2007, Section 3.2]).

To construct the Laplace approximation to the GLMM likelihood, each of the integrals in (1.26) has to be approximated. Setting

$$h(\mathbf{u}_i) = -\left(\sum_{j=1}^{n_i} \{w_{ij}[y_{ij}\theta_{ij} - b(\theta_{ij})] + c(y_{ij})\} - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i\right)$$

with  $\theta_{ij} = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \mathbf{z}_{ij}^T \mathbf{D} \mathbf{u}_i$  and  $m = 1$  and applying (1.29) we get the LA log-likelihood

$$l_{LA}(\boldsymbol{\psi}; \mathbf{y}) = - \sum_{i=1}^n h(\hat{\mathbf{u}}_i) - \frac{1}{2} \sum_{i=1}^n \log \mathbf{det}[h''(\hat{\mathbf{u}}_i)] \quad (1.30)$$

with

$$h''(\hat{\mathbf{u}}_i) = \mathbf{I}_q + \mathbf{D}^T \left( \sum_{j=1}^{n_i} w_{ij} b''(\hat{\theta}_{ij}) \mathbf{z}_{ij} \mathbf{z}_{ij}^T \right) \mathbf{D} = \mathbf{I}_q + \mathbf{D}^T \boldsymbol{\Delta}_i \mathbf{D}. \quad (1.31)$$

To construct  $l_{LA}(\boldsymbol{\psi}; \mathbf{y})$  we need to find  $\hat{\mathbf{u}}_i$ s as a function of the parameter  $\boldsymbol{\psi}$ . Therefore, in practice, an iterative algorithm of maximizing of  $l_{LA}(\boldsymbol{\psi}; \mathbf{y})$  with respect to  $\boldsymbol{\psi}$  includes an additional step at which  $\hat{\mathbf{u}}_i$ s are calculated given the current value of  $\boldsymbol{\psi}$ . In Chapter 2 we will develop a higher-order Laplace approximation for GLMM likelihood.

### 1.3.4 Penalized Quasi-Likelihood

Penalized Quasi-Likelihood (PQL) was considered in Green [1987], Green [1990], Schall [1991], Breslow and Clayton [1993], and Wolfinger and O'Connell [1993] and can be seen as a certain simplification of LA. The PQL approach ignores the last term of (1.30) and considers the PQL likelihood

$$l_{PQL}(\boldsymbol{\beta}, \mathbf{u}_1, \dots, \mathbf{u}_n) = - \sum_{i=1}^n h(\boldsymbol{\beta}, \mathbf{u}_i) \quad (1.32)$$

as a function of  $(\boldsymbol{\beta}, \mathbf{u}_1, \dots, \mathbf{u}_n)$  holding the matrix  $\mathbf{D}$  (or vector  $\boldsymbol{\sigma}$ ) fixed. Following [Demidenko, 2004, Section 7.7] an estimate of  $\boldsymbol{\Sigma} = \mathbf{D} \mathbf{D}^T$  can be obtained as the solution of the following matrix equation

$$\boldsymbol{\Sigma} = \bar{\mathbf{U}} + \frac{1}{n} \sum_{i=1}^n (\boldsymbol{\Sigma}^{-1} + \boldsymbol{\Delta}_i)^{-1} \quad (1.33)$$

where  $\bar{\mathbf{U}} = 1/n \sum_{i=1}^n \hat{\mathbf{u}}_i \hat{\mathbf{u}}_i^T$ . In practice, the PQL fitting algorithm is as follows. Starting with a reasonable value  $\boldsymbol{\Sigma}^0$  find  $\boldsymbol{\beta}^{(1)}$  and  $(\hat{\mathbf{u}}_1^{(1)}, \dots, \hat{\mathbf{u}}_n^{(1)})$  maximizing (1.32) given  $\boldsymbol{\Sigma}^0$ . Update  $\boldsymbol{\Sigma}^1$  using (1.33) with  $\boldsymbol{\Sigma}^0$  on the right hand side. Then iterate until convergence.

Due to the approximations involved in derivations, the PQL estimator can be severely biased. In fact, it has been shown theoretically that the PQL estimator is inconsistent (Jiang [1998]). However, inclusion of second-order terms reduces the bias. Breslow and Lin [1995] and Lin and Breslow [1996] proposed a bias correction to PQL which uses a second-order Laplace approximation and showed a significant improvement compared to the first-order PQL estimator, originally proposed in Breslow and Clayton [1993].

### 1.3.5 Simulated Maximum Likelihood

We now consider the next group of approximations based on Monte Carlo simulations. We will start with Simulated Maximum Likelihood (SML) considered in Geyer and Thompson [1992], Durbin and Koopman [1997], Lee [1999], and Booth et al. [2001] among others. The integrals

$$\mathfrak{G}_i = \int_{\mathbb{R}^q} f(\mathbf{y}_i | \mathbf{u}_i; \boldsymbol{\psi}) \phi(\mathbf{u}_i, \mathbf{I}_q) d\mathbf{u}_i \quad i = 1, \dots, n \quad (1.34)$$

can be rewritten as

$$\mathfrak{G}_i = \int_{\mathbb{R}^q} \frac{f(\mathbf{y}_i | \mathbf{u}_i; \boldsymbol{\psi}) \phi(\mathbf{u}_i, \mathbf{I}_q)}{h(\mathbf{u}_i)} h(\mathbf{u}_i) d\mathbf{u}_i, \quad i = 1, \dots, n \quad (1.35)$$

for any probability density function  $h(\mathbf{u}_i)$  having the same support as  $\phi(\mathbf{u}_i, \mathbf{I}_q)$ . The density  $h(\mathbf{u}_i)$  is called an *importance sampler*. An i.i.d. MC sample  $\{\mathbf{u}_i^{(1)}, \dots, \mathbf{u}_i^{(M_i)}\}$  is generated from  $h(\mathbf{u}_i)$  and the integral (1.35) is approximated by the MC average

$$\mathfrak{G}_i^{SML} = \frac{1}{M_i} \sum_{m_i=1}^{M_i} \frac{f(\mathbf{y}_i | \mathbf{u}_i^{(m_i)}; \boldsymbol{\psi}) \phi(\mathbf{u}_i^{(m_i)}, \mathbf{I}_q)}{h(\mathbf{u}_i^{(m_i)})}, \quad i = 1, \dots, n. \quad (1.36)$$

Combining averages (1.36) we get SML likelihood

$$L_{SML}(\boldsymbol{\psi}; \mathbf{y}) = \sum_{i=1}^n \frac{1}{M_i} \sum_{m_i=1}^{M_i} \frac{f(\mathbf{y}_i | \mathbf{u}_i^{(m_i)}; \boldsymbol{\psi}) \phi(\mathbf{u}_i^{(m_i)}, \mathbf{I}_q)}{h(\mathbf{u}_i^{(m_i)})} \quad (1.37)$$

The SML estimator  $\hat{\psi}_{SML}$  is the maximum of the SML likelihood (1.37). Notice that (1.37) always gives an unbiased estimator of the GLMM likelihood. However, its variability is determined by the choice of importance sampler  $h(\mathbf{u}_i)$  (see Owen and Zhou [2000], Robert and Casella [2004]), as well as the sample sizes,  $M_i$ .

### 1.3.6 Quasi-Monte Carlo method

Quasi-Monte Carlo (QMC) methods have received a lot of attention recently. Particularly, Kuo et al. [2008] adapted QMC to the GLMM setting. In the QMC approach, the integral of interest

$$\mathbf{I}(h) = \int_{\mathbb{R}^q} h(\mathbf{u}) d\mathbf{u} \quad (1.38)$$

is transformed into an integral over the unit cube

$$\mathbf{I}(h) = \int_{[0,1]^q} h(\mathfrak{F}^{-1}(\mathbf{v})) d\mathbf{v} \quad (1.39)$$

with the use of a transformation  $\mathbf{v} = \mathfrak{F}(\mathbf{u})$  where  $\mathfrak{F} : \mathbb{R}^q \rightarrow [0, 1]^q$ . Then the QMC approximation is constructed as QMC average

$$\mathbf{I}(h)_{QMC} = \frac{1}{M} \sum_{i=1}^M h(\mathfrak{F}^{-1}(\mathbf{v}_m)) \quad (1.40)$$

where  $\{\mathbf{v}_1, \dots, \mathbf{v}_M\}$  is a low-discrepancy QMC sequence from  $[0, 1]^q$ . The low-discrepancy guarantees that a rate of convergence is at least  $O(M^{-1}(\log M)^q)$  which dominates that of a standard MC approach,  $O(M^{-1/2})$ . This, as well as the ease of the generating a low-discrepancy QMC sequence, are two major advantages of QMC over simple MC methods. Referring the reader for more details to Kuo et al. [2008], we will discuss two main findings of their paper. First, as one would expect, the transformation  $\mathfrak{F}$  plays a crucial role as it controls the properties of the transformed integrand. The

other finding is that for small dimensions such as  $q = 25$ , QMC dramatically outperforms simple MC. However, as  $q$  increases to 200, the superiority of QMC over simple MC is diminished.

Here, we briefly reiterate the main differences between the approach suggested in this dissertation and simple MC methods. The first advantage stems from the fact that the complexity of evaluating the GLMM integrand usually dominates that of generating the Monte Carlo and Quasi-Monte Carlo points. Our approach exploits a partial linearity of the integrand by using very structured configurations of the cubature knots which results in a dramatic reduction of the computational complexity. The other advantage is that the cubature knots are chosen in a way which increases the polynomial accuracy of the approximation. In other words, although the rate of convergence is still  $O(M^{-1/2})$  the constant at  $M^{-1/2}$  is much smaller than in simple MC methods. All these features will be considered in much more detail in Chapter 2.

## 1.4 Monte Carlo Expectation Maximization

The expectation maximization (EM) algorithm introduced in the seminal work of Dempster et al. [1977] is a widely-used iterative method for finding maximum likelihood estimates when there is missing or unobserved data. The EM algorithm can be applied in the GLMM context because the random effects are unobserved. The algorithm includes two steps at each iteration, an E-step and an M-step. Let  $\boldsymbol{\psi}^{(s)}$  denote the value of the parameter after iteration  $s$ . Then the E-step at iteration  $s + 1$  involves the computation of the so-called  $Q$ -function,

$$Q(\boldsymbol{\psi}|\boldsymbol{\psi}^{(s)}) = E\left[l(\boldsymbol{\psi}; \mathbf{y}, \mathbf{u})|\mathbf{y}; \boldsymbol{\psi}^{(s)}\right],$$

where

$$l(\boldsymbol{\psi}; \mathbf{y}, \mathbf{u}) = \log f(\mathbf{y}, \mathbf{u}; \boldsymbol{\psi})$$

is the *complete data* loglikelihood for parameter  $\boldsymbol{\psi}$ . The M-step consists of finding  $\boldsymbol{\psi}^{(s+1)}$  which maximizes the Q-function; that is

$$\boldsymbol{\psi}^{(s+1)} = \arg \max_{\boldsymbol{\psi} \in \boldsymbol{\Psi}} Q(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)})$$

Under mild regularity conditions the observable likelihood function (1.24) is non-decreasing when evaluated along the EM sequence  $\{\boldsymbol{\psi}^{(s)}\}_{s=0}^{\infty}$  [see e.g. Wu, 1983]. Hence, the sequence converges to a local maximum of the likelihood surface.

Let us recall that the complete data loglikelihood is given by

$$l(\boldsymbol{\psi}; \mathbf{y}, \mathbf{u}) = \sum_{i=1}^n \left( \sum_{j=1}^{n_i} \{w_{ij}[\theta_{ij}y_{ij} - b(\theta_{ij})] + c(y_{ij})\} - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i \right)$$

Hence, the Q-function calculated at the iteration  $s + 1$  is

$$Q(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)}) = \sum_{i=1}^n E \left[ \sum_{j=1}^{n_i} \{w_{ij}[\theta_{ij}y_{ij} - b(\theta_{ij})] + c(y_{ij})\} - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i | \mathbf{y}_i; \boldsymbol{\psi}^{(s)} \right]$$

However, part of this expression,

$$\sum_{i=1}^n E \left[ \sum_{j=1}^{n_i} w_{ij} c(y_{ij}) - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i | \mathbf{y}_i; \boldsymbol{\psi}^{(s)} \right],$$

can be eliminated because it does not depend on the parameter  $\boldsymbol{\psi}$ , and has no effect on the M-step. Therefore, without loss of generality, we shall consider the reduced Q-function,

$$Q(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)}) = \sum_{i=1}^n E \left[ \sum_{j=1}^{n_i} w_{ij} [\theta_{ij}y_{ij} - b(\theta_{ij})] | \mathbf{y}_i; \boldsymbol{\psi}^{(s)} \right],$$

in what follows.

Notice that

$$Q(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)}) = \sum_{i=1}^n E \left[ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}) | \mathbf{y}_i; \boldsymbol{\psi}^{(s)} \right] \quad (1.41)$$

where

$$a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}) = \sum_{j=1}^{n_i} w_{ij} [\theta_{ij} y_{ij} - b(\theta_{ij})].$$

Hence, the  $i$ th term in the  $Q$ -function is given by

$$E \left[ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}) | \mathbf{y}_i; \boldsymbol{\psi}^{(s)} \right] = \int_{\mathbb{R}^q} a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}) f(\mathbf{u}_i | \mathbf{y}_i; \boldsymbol{\psi}^{(s)}) d\mathbf{u}_i, \quad (1.42)$$

where

$$f(\mathbf{u}_i | \mathbf{y}_i; \boldsymbol{\psi}^{(s)}) = \frac{f(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)})}{f(\mathbf{y}_i; \boldsymbol{\psi}^{(s)})} = \frac{\exp \left\{ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)}) - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i \right\}}{\int_{\mathbb{R}^q} \exp \left\{ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)}) - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i \right\} d\mathbf{u}_i} \quad (1.43)$$

As noted earlier the denominator in (1.43) is generally analytically intractable in the GLMM context. In such cases Wei and Tanner [1990] suggested approximating the expectations in the  $Q$ -function by Monte Carlo averages, resulting in the so-called MCEM algorithm. For example, if it is possible to generate i.i.d. vectors  $\{\mathbf{u}_i^{(1)}, \dots, \mathbf{u}_i^{(M)}\}$  from (1.43), a Monte Carlo approximation to  $Q$  is given by

$$\hat{Q}(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)}) = \frac{1}{M} \sum_{i=1}^n \sum_{k=1}^M a(\mathbf{y}_i, \mathbf{u}_i^{(k)}; \boldsymbol{\psi}) = \frac{1}{M} \sum_{i=1}^n \sum_{k=1}^M \sum_{j=1}^{n_i} w_{ij} [\theta_{ij}^{(k)} y_{ij} - b(\theta_{ij}^{(k)})] \quad (1.44)$$

where  $\theta_{ij}^{(k)}$  involves the parameter vector,  $\boldsymbol{\psi}$ , via the identities,

$$\theta_{ij}^{(k)} = (b')^{-1}[\mu_{ij}^{(k)}], \quad \mu_{ij}^{(k)} = g^{-1}(\eta_{ij}^{(k)}), \quad \text{and} \quad \eta_{ij}^{(k)} = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \boldsymbol{\xi}_{ij}^{(k)T} \boldsymbol{\sigma} = \tilde{\mathbf{x}}_{ij}^{(k)T} \boldsymbol{\psi}.$$

Notice that  $\hat{Q}(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)})$  has the form of the loglikelihood of a GLM, and hence the M-step can be performed by using the standard IRLS fitting algorithm [McCullagh and Nelder, 1989, Section 2.5].

However, direct i.i.d. sampling from (1.43) is usually not feasible. To overcome this, McCulloch (1994,1997), suggested using MCMC with stationary distribution (1.43) to approximate the E-step. In contrast, two i.i.d sampling schemes, rejection sampling and importance sampling, were proposed by Booth and Hobert [1999] to generate a Monte Carlo sample following (1.43).

It should be noted that MCEM is not deterministic. One must increase the MC sample size to decrease Monte Carlo error and to ensure convergence. An automated rule was described in Booth and Hobert [1999] where estimates of Monte Carlo error were used to determine if the Monte Carlo sample size is sufficient. Caffo et al. [2005] suggested another data-driven algorithm based on the EM ascent property. The algorithm not only determines the sample size for each iteration of MCEM but also provides a convenient stopping rule by monitoring the change in the  $Q$ -function.

### 1.4.1 Ascent-based MCEM and the stopping rule

Booth and Hobert [1999] and Caffo et al. [2005] propose methods for controlling Monte Carlo sample size when implementing MCEM. The approach of Caffo et al. is based on the ascent property of the EM algorithm, that the loglikelihood increases at each iteration. More specifically,

$$\Delta Q^{(s+1)} = Q(\boldsymbol{\psi}^{(s+1)}|\boldsymbol{\psi}^{(s)}) - Q(\boldsymbol{\psi}^{(s)}|\boldsymbol{\psi}^{(s)}) \geq 0$$

implies, via an application of Jensen's inequality, that

$$l(\boldsymbol{\psi}^{(s+1)}|\mathbf{y}) \geq l(\boldsymbol{\psi}^{(s)}|\mathbf{y}). \quad (1.45)$$

However, in MCEM  $\Delta Q^{(s+1)}$  is approximated by

$$\Delta \hat{Q}^{(s+1)} = \hat{Q}(\boldsymbol{\psi}^{(s+1)}|\boldsymbol{\psi}^{(s)}) - \hat{Q}(\boldsymbol{\psi}^{(s)}|\boldsymbol{\psi}^{(s)})$$

and the inequality,  $\Delta \hat{Q}^{(s+1)} \geq 0$  no longer guarantees (1.45).

In fact, since the value of  $\Delta \hat{Q}^{(s+1)}$  is a ratio of two Monte Carlo means, its standard error,  $\sigma_{\Delta \hat{Q}}$ , can be estimated using the delta method [Stuart and Ord, 1994, 10.5-7], and this can be used to construct a lower confidence limit for  $\Delta Q^{(s+1)}$  of the form

$$\Delta \hat{Q}^{(s+1)} - z_{\gamma_1} \hat{\sigma}_{\Delta \hat{Q}}. \quad (1.46)$$



The approach advocated by Caffo et al. is to compute a lower bound of the form (1.46) after each iteration. If the lower bound is positive, the algorithm continues as usual. However, if the lower bound is negative,  $\psi^{(s+1)}$  calculated with Monte Carlo sample size  $m$  is rejected and the MCEM iteration is repeated with an increased Monte Carlo sample size  $m + m/k$ , for some  $k$ . Caffo et al. [2005, equation 15] suggest that the increase should be determined by the standard sample size formula for a formal test of  $\Delta Q^{(s+1)} = 0$  versus  $\Delta Q^{(s+1)} > 0$  with type 1 error equal to  $\alpha$  and type 2 error equal to  $\beta$ , using estimates of  $\Delta Q$  and  $\sigma_{\Delta Q}$  from the previous iteration

$$m_{s+1,start} = \max\{m_{s,start}, \sigma_{\Delta Q}^2 (z_\alpha + z_\beta)^2 / (\Delta \hat{Q}^{(s)})^2\} \quad (1.47)$$

The deterministic EM algorithm is usually terminated when changes in the  $Q$ -function (and hence in the loglikelihood) are negligible. Even though the  $Q$ -function is not observed directly in implementations of the MCEM algorithm, one can calculate an upper confidence limit for  $\Delta Q$  after each iteration, in a similar manner to the lower limit [Caffo et al., 2005, equation 13]. The algorithm may then be judged to have converged if the upper bound is negligibly small (but non-negative), that is,

$$\Delta \hat{Q}^{(s+1)} + z_{\gamma_2} \hat{\sigma}_{\Delta Q} \leq \epsilon. \quad (1.48)$$

In addition to (1.48) we require the relative change in the parameter estimates at the  $(s + 1)$ th iteration to be sufficiently small; that is

$$\max_{1 \leq i \leq p+q^*} \frac{|\psi_i^{(s+1)} - \psi_i^{(s)}|}{|\psi_i^{(s)}| + \delta_1} \leq \delta_2 \quad (1.49)$$

Hence, the convergence is declared if both (1.48) and (1.49) hold.

## CHAPTER 2

### MCEM-SR AND EM-LA<sub>2</sub> FOR GLMM

#### 2.1 MCEM-SR

A serious drawback of implementations of MCEM to date, in the GLMM context, is that the MC sample size required for convergence can be so large as to make the algorithm impractical. In this part of the dissertation, we describe a new implementation of MCEM, MCEM-SR, using the spherical-radial integration rule by Genz and Monahan(1997, 1998 and 1999), which can dramatically reduce the MC sample size required for convergence.

##### 2.1.1 The SR approximation

Recall that at the E-step of the EM algorithm we want to approximate the  $Q$ -function given by (1.41). In view of (1.42) and (1.43) the  $i$ th term in it can be presented as an integral of the form

$$I(c; p) = \frac{\int_{\mathbb{R}^q} c(\mathbf{u})p(\mathbf{u})d\mathbf{u}}{\int_{\mathbb{R}^q} p(\mathbf{u})d\mathbf{u}},$$

where  $p(\mathbf{u})$  is an unnormalized probability density and  $c(\mathbf{u})$  is an integrable function with respect to  $p(\mathbf{u})$ . The SR approximation method can be described in four steps.

1. *Standardization of the density.*

Let  $\hat{\mathbf{u}}$  denote the mode of the unnormalized density  $p(\mathbf{u})$ , and let  $\mathbf{H} = -\partial^2 \log p(\hat{\mathbf{u}})/\partial \mathbf{u} \partial \mathbf{u}^T$  be the negative of its Hessian matrix evaluated at the mode.

We suppose that  $\mathbf{H}$  is positive definite, and denote its Cholesky decomposition by  $\mathbf{H}^{1/2}(\mathbf{H}^{1/2})^T$ . After changing the variable of integration from  $\mathbf{u}$  to  $\tilde{\mathbf{u}} = \mathbf{H}^{1/2}(\mathbf{u} - \hat{\mathbf{u}})$  the integral becomes

$$I(c; p) = \frac{\det(\mathbf{H}^{1/2}) \int_{\mathbb{R}^q} \tilde{c}(\tilde{\mathbf{u}}) \tilde{p}(\tilde{\mathbf{u}}) d\tilde{\mathbf{u}}}{\det(\mathbf{H}^{1/2}) \int_{\mathbb{R}^q} \tilde{p}(\tilde{\mathbf{u}}) d\tilde{\mathbf{u}}} = \frac{\int_{\mathbb{R}^q} \tilde{c}(\tilde{\mathbf{u}}) \tilde{p}(\tilde{\mathbf{u}}) d\tilde{\mathbf{u}}}{\int_{\mathbb{R}^q} \tilde{p}(\tilde{\mathbf{u}}) d\tilde{\mathbf{u}}},$$

where  $\tilde{c}(\tilde{\mathbf{u}}) = c(\hat{\mathbf{u}} + \mathbf{H}^{-1/2}\tilde{\mathbf{u}})$  and  $\tilde{p}(\tilde{\mathbf{u}}) = p(\hat{\mathbf{u}} + \mathbf{H}^{-1/2}\tilde{\mathbf{u}})$ . The density  $\tilde{p}$  is standardized in the sense that it attains its maximum at  $\mathbf{0}$  and  $-\tilde{\mathbf{H}}(\mathbf{0}) = -\partial^2 \log \tilde{p}(\mathbf{0}) / \partial \tilde{\mathbf{u}} \partial \tilde{\mathbf{u}}^T = \mathbf{I}_q$ .

## 2. The spherical-radial transformation.

At this step we change the variables of integration from  $\tilde{\mathbf{u}}$  to  $(r, \mathbf{s})$ , where  $r$  is the radius, and  $\mathbf{s}$  is a point on the surface of the unit sphere  $U_q$ ; that is,  $\tilde{\mathbf{u}} = r\mathbf{s}$ , and  $\mathbf{s}^T \mathbf{s} = 1$ . The integral now becomes

$$I(c; p) = \frac{\int_0^\infty \int_{U_q} \tilde{c}(r\mathbf{s}) \tilde{p}(r\mathbf{s}) r^{q-1} d\mathbf{s} dr}{\int_0^\infty \int_{U_q} \tilde{p}(r\mathbf{s}) r^{q-1} d\mathbf{s} dr} \quad (2.1)$$

According to Genz and Monahan [1997] “the value of changing to  $(r, \mathbf{s})$  is that the most common failure of the normal approximation to the posterior appears in the tails, goes after the SR transformation to the radius  $r$ ”. Notice that, if we denote

$$\mathfrak{S}_{\text{num}}(r) = \int_{U_q} \tilde{c}(r\mathbf{s}) \tilde{p}(r\mathbf{s}) d\mathbf{s} \quad \text{and} \quad \mathfrak{S}_{\text{den}}(r) = \int_{U_q} \tilde{p}(r\mathbf{s}) d\mathbf{s}, \quad (2.2)$$

then

$$I(c; p) = \frac{I_{\text{num}}(c; p)}{I_{\text{den}}(p)} = \frac{\int_0^\infty \mathfrak{S}_{\text{num}}(r) r^{q-1} dr}{\int_0^\infty \mathfrak{S}_{\text{den}}(r) r^{q-1} dr}.$$

## 3. Approximation of the spherical integral.

Given  $r$ , the inner spherical integral  $\mathfrak{S}_{\text{num}}(r)$  may be approximated by

$$\hat{\mathfrak{S}}_{\text{num}}(r) = \frac{1}{M_3} \sum_{m_3=1}^{M_3} \sum_{k=1}^d \sum_{l=1}^{T_k} \nu_{kl} \tilde{c}(r \mathbf{Q}_{m_3} \mathbf{v}_{kl}) \tilde{p}(r \mathbf{Q}_{m_3} \mathbf{v}_{kl}), \quad (2.3)$$

where  $\mathbf{Q}_1, \dots, \mathbf{Q}_{M_3}$  are i.i.d. random orthogonal matrices of dimension  $q \times q$ ,  $\{\mathbf{v}_{kl}\}$  are points on the  $q$ -dimensional unit sphere, and  $\{\nu_{kl}\}$  are corresponding

weights chosen such that  $E\hat{\mathfrak{G}}_{\text{num}}(r) = \mathfrak{G}_{\text{num}}(r)$ . We will review some possible choices of  $\{\mathbf{v}_{kl}\}$  and  $\{\nu_{kl}\}$  in the next section.

#### 4. Approximation of the radial integral.

The remaining one dimensional radial integral,

$$\mathfrak{R} = \int_0^\infty \hat{\mathfrak{G}}_{\text{num}}(r)r^{q-1}dr \quad (2.4)$$

can be approximated either by deterministic or randomized quadratures. In both cases, the approximation may be written as

$$\hat{\mathfrak{R}} = \frac{1}{M_1} \sum_{m_1=1}^{M_1} \sum_{m_2=1}^{M_2} \gamma_{m_1 m_2} \hat{\mathfrak{G}}_{\text{num}}(r_{m_1 m_2}) \quad (2.5)$$

Randomized rules give unbiased estimates of the radial integral (2.4) and, depending on the order of the rule, is exact for any polynomial of this degree. In contrast, deterministic quadratures are known to have a fixed error of approximation. We will review both types of approximations in a following section.

Now, if we denote

$$\varrho_{m_1 m_2 m_3 kl} = r_{m_1 m_2} \mathbf{Q}_{m_1 m_2 m_3} \mathbf{v}_{kl},$$

then the SR approximation of the numerator integral in (2.1) is given by

$$I_{\text{num}}^{SR}(c; p) = \frac{1}{M_1 M_3} \sum_{m_1, m_2, m_3, k, l} \gamma_{m_1 m_2} \nu_{kl} \tilde{c}(\varrho_{m_1 m_2 m_3 kl}) \tilde{p}(\varrho_{m_1 m_2 m_3 kl}). \quad (2.6)$$

Setting  $\tilde{c} \equiv 1$ , we get the approximation to the denominator integral in (2.1)

$$I_{\text{den}}^{SR}(p) = \frac{1}{M_1 M_3} \sum_{m_1, m_2, m_3, k, l} \gamma_{m_1 m_2} \nu_{kl} \tilde{p}(\varrho_{m_1 m_2 m_3 kl}). \quad (2.7)$$

Combining approximations to all the integrals in (1.41) results in a Monte Carlo SR approximation to the  $Q$ -function. Notice, that since the  $Q$ -function involves a ratio of integrals, the approximation is not unbiased. However, the Law of Large Numbers ensures asymptotic unbiasedness as long as a randomized quadrature rule is used and  $M_1$  goes to infinity. In particular, the approximation converges as  $M_1 \rightarrow \infty$  with  $M_3 = 1$ .

## 2.1.2 Approximation of the radial integral

We will follow Genz and Monahan (1997, 1998 and 1999) and consider three stochastic integration rules for the integral

$$\mathfrak{R} = \int_0^\infty \hat{\mathfrak{G}}(r) r^{q-1} dr \quad (2.8)$$

resulting in approximations of the form

$$\hat{\mathfrak{R}} = \frac{1}{M_1} \sum_{m_1=1}^{M_1} \sum_{m_2=1}^{M_2} \gamma_{m_1 m_2} \hat{\mathfrak{G}}(r_{m_1 m_2}). \quad (2.9)$$

The first order rule is determined by the system

$$\begin{cases} M_2 = 1, & m_1 = 1, \dots, M_1 \\ r_{m_1 1} = \chi_q \\ \gamma_{m_1 1} = 2^{q/2} \Gamma(q/2) \exp(r_{m_1 1}^2/2), \end{cases} \quad (2.10)$$

where the equality  $r_{m_1 1} = \chi_q$  in (2.10) means that  $\{r_{11}, \dots, r_{M_1 1}\}$  are  $\chi_q$  i.i.d. random variables. The first order rule (2.10) is unbiased for all functions  $\hat{\mathfrak{G}}(r)$  and exact if the function  $\hat{\mathfrak{G}}(r)e^{-r^2/2}$  is linear.

The third order rule is given by

$$\begin{cases} M_2 = 2, & m_1 = 1, \dots, M_1 \\ (r_{m_1 1}, r_{m_1 2}) = (0, \chi_{q+2}) \\ \gamma_{m_1 1} = 2^{q/2} \Gamma(q/2) (1 - q/r_{m_1 2}^2) \\ \gamma_{m_1 2} = 2^{q/2} \Gamma(q/2) \exp(r_{m_1 2}^2/2) q/r_{m_1 2}^2 \end{cases} \quad (2.11)$$

and requires generation of the sample  $\{r_{12}, \dots, r_{M_1 2}\}$  which are  $\chi_{q+2}$  i.i.d. random variables. It is also unbiased for all functions  $\hat{\mathfrak{G}}(r)$ . It is exact if the function  $\hat{\mathfrak{G}}(r)e^{-r^2/2}$  is a polynomial of third degree.

The last rule we consider is the fifth order rule. It is given by

$$\left\{ \begin{array}{l} M_2 = 3, \quad m_1 = 1, \dots, M_1 \\ (r_{m_11}, r_{m_12}, r_{m_13}) = (0, \mathbf{u}_{m_1} \sin(\arcsin(\mathbf{v}_{m_1})/2), \mathbf{u}_{m_1} \cos(\arcsin(\mathbf{v}_{m_1})/2)) \\ (\mathbf{u}_{m_1}, \mathbf{v}_{m_1}) = (\chi_{2q+7}, \mathbf{Beta}(q+2, 3/2)) \\ \gamma_{m_11} = 2^{q/2} \Gamma(q/2) (1 - q(r_{m_12}^2 + r_{m_13}^2 - (q+2)) / [r_{m_12}^2 r_{m_13}^2]) \\ \gamma_{m_12} = 2^{q/2} \Gamma(q/2) \exp(r_{m_12}^2/2) q(q+2 - r_{m_13}^2) / [r_{m_12}^2 (r_{m_12}^2 - r_{m_13}^2)] \\ \gamma_{m_13} = 2^{q/2} \Gamma(q/2) \exp(r_{m_13}^2/2) q(q+2 - r_{m_12}^2) / [r_{m_13}^2 (r_{m_13}^2 - r_{m_12}^2)]. \end{array} \right. \quad (2.12)$$

To implement this rule, two i.i.d. samples have to be generated,  $\{\mathbf{u}_{m_1}\}_{m_1=1}^{M_1}$  from  $\chi_{2q+7}$  distribution and  $\{\mathbf{v}_{m_1}\}_{m_1=1}^{M_1}$  following a  $\mathbf{Beta}(q+2, 3/2)$  distribution. This rule provides an unbiased estimator and is exact when the function  $\tilde{\mathfrak{S}}(r)e^{-r^2/2}$  is a polynomial of fifth degree.

Genz and Monahan [1998] derived stochastic integration rules of arbitrary order. However, in practice the higher order rules are hard to implement. Finally, we note that Gauss-Hermite quadratures (Abramowitz and Stegun [1965]) can be easily used to construct an approximation of the form (2.9). However, deterministic rules do not allow to estimate and control the error of the approximation. Therefore, we do not include them in our approach.

### 2.1.3 Approximation of the spherical integral

Now, let us consider stochastic cubature rules approximating the integral

$$\mathfrak{S} = \int_{U_q} h(\mathbf{s}) d\mathbf{s}. \quad (2.13)$$

with

$$\hat{\mathfrak{S}} = \frac{1}{M_3} \sum_{m_3=1}^{M_3} \sum_{k=1}^d \sum_{l=1}^{T_k} \nu_{kl} h(\mathbf{Q}_{m_3} \mathbf{v}_{kl}). \quad (2.14)$$

The rules reviewed in this section are from Mysovskih [1981]. All the stochastic rules of the form (2.14) considered below provide unbiased estimators of (2.13). In addition, the approximation (2.14) provided by the  $m$ th order rule is exact as long as the function  $h(\mathbf{s})$  is a polynomial of  $m$ th degree. Let  $O_q G(a_1, \dots, a_q)$  denote a set of vectors containing all possible permutations and sign changes of the coordinates of the vector  $(a_1, \dots, a_q)$ . Let  $\mu(U_q)$  denote the surface area of the unit sphere which is equal to  $2\pi^{q/2}/\Gamma(q/2)$ .

The third order rule

$$\left\{ \begin{array}{l} d = 1 \\ T_1 = 2q \\ \{\mathbf{v}_{11}, \dots, \mathbf{v}_{1T_1}\} = O_q G(1, 0, 0, \dots, 0) \\ \nu_{1l} = \mu(U_q)/(2q), \quad l = 1, \dots, T_1 \end{array} \right. \quad (2.15)$$

is valid for  $q \geq 2$ . The fifth order rule is given by

$$\left\{ \begin{array}{l} d = 2 \\ T_1 = 2q, T_2 = 2q(q - 1) \\ \{\mathbf{v}_{11}, \dots, \mathbf{v}_{1T_1}\} = O_q G(1, 0, 0, \dots, 0) \\ \{\mathbf{v}_{21}, \dots, \mathbf{v}_{2T_2}\} = O_q G(1/\sqrt{2}, 1/\sqrt{2}, 0, \dots, 0) \\ \nu_{1l} = (4 - q)\mu(U_q)/(2q(q + 2)), \quad l = 1, \dots, T_1 \\ \nu_{2l} = \mu(U_q)/(q(q + 2)), \quad l = 1, \dots, T_2 \end{array} \right. \quad (2.16)$$

and can be applied when  $q \geq 3$ . If  $q = 4$  the weights  $\nu_{1l} = 0$  and the total number of knots is equal to  $T_2 = 24$ . The seventh order rule is

$$\left\{ \begin{array}{l} d = 3 \\ T_1 = 2q, T_2 = 2q(q - 1), T_3 = 2q(2q^2 - 6q + 4)/3 \\ \{\mathbf{v}_{11}, \dots, \mathbf{v}_{1T_1}\} = O_q G(1, 0, 0, \dots, 0) \\ \{\mathbf{v}_{21}, \dots, \mathbf{v}_{2T_2}\} = O_q G(1/\sqrt{2}, 1/\sqrt{2}, 0, \dots, 0) \\ \{\mathbf{v}_{31}, \dots, \mathbf{v}_{3T_3}\} = O_q G(1/\sqrt{3}, 1/\sqrt{3}, 1/\sqrt{3}, 0, \dots, 0) \\ \nu_{1l} = (q^2 - 9q + 38)\mu(U_q)/(4q(q + 2)(q + 4)), \quad l = 1, \dots, T_1 \\ \nu_{2l} = 2(5 - q)\mu(U_q)/(q(q + 2)(q + 4)), \quad l = 1, \dots, T_2 \\ \nu_{3l} = 27\mu(U_q)/(8q(q + 2)(q + 4)), \quad l = 1, \dots, T_3 \end{array} \right. \quad (2.17)$$

and needs  $q$  to be greater than or equal three. If  $q = 5$  the  $\nu_{2l} = 0$  so the total number of knots  $N = 90$ . The last rule, the ninth order rule, is determined by the system

$$\left\{ \begin{array}{l} d = 4 \\ T_1 = 2q, T_2 = 2q(q - 1) \\ T_3 = 2q(2q^2 - 6q + 4)/3, T_4 = 2q(q^3 - 6q^2 + 14q - 9)/3 \\ \{\mathbf{v}_{11}, \dots, \mathbf{v}_{1T_1}\} = O_q G(1, 0, 0, \dots, 0) \\ \{\mathbf{v}_{21}, \dots, \mathbf{v}_{2T_2}\} = O_q G((1 - \mathfrak{t})/\sqrt{2\mathfrak{t}^2 - 2\mathfrak{t} + 1}, \mathfrak{t}/\sqrt{2\mathfrak{t}^2 - 2\mathfrak{t} + 1}, 0, 0, \dots, 0) \\ \{\mathbf{v}_{31}, \dots, \mathbf{v}_{3T_3}\} = O_q G(1/\sqrt{3}, 1/\sqrt{3}, 1/\sqrt{3}, 0, \dots, 0) \\ \{\mathbf{v}_{41}, \dots, \mathbf{v}_{4T_4}\} = O_q G(1/2, 1/2, 1/2, 1/2, 0, \dots, 0) \\ \nu_{1l} = (-q^5 + 26q^4 - 437q^3 + 3988q^2 - 18732q + 31536)\mathfrak{z}/(12(q^2 - 11q + 36)) \\ \nu_{2l} = (q^2 - 11q + 42)^2\mathfrak{z}/(q^2 - 11q + 36), \quad l = 1, \dots, T_2 \\ \nu_{3l} = 81(6 - q)\mathfrak{z}/8, \quad l = 1, \dots, T_3 \\ \nu_{4l} = 16\mathfrak{z}, \quad l = 1, \dots, T_4, \end{array} \right. \quad (2.18)$$



with

$$\begin{aligned} \mathbf{t} &= (1 - \sqrt{(1 - \mathfrak{s})/(1 + \mathfrak{s})})/2 \\ \mathfrak{s} &= \sqrt{(q^2 - 11q + 36)/(q^2 - 11q + 42)} \\ \mathfrak{z} &= \mu(U_q)/(q(q + 2)(q + 4)(q + 6)) \end{aligned}$$

If  $q = 3$  the  $\mathbf{v}_{4l}$  knots do not exist. When  $q = 6$  the number of knots equals 372 as  $\nu_{3l} = 0$ .

To construct a higher order rule, the knots  $\mathbf{v}_{kl}$  (potentially depending on a few extra parameters) should be chosen and then the weights  $\nu_{kl}$  can be determined as a solution to a system of algebraic equations (see Mysovskih [1981]). Solving such a system remains an open problem of numerical integration. However, for practical purposes, for any particular combination of the dimension  $q$  and the order of the rule  $m$ , the system can be solved numerically. This provides a potential way of expanding the set of rules presented above.

## 2.1.4 M-Step

In this section we will discuss the maximization of the approximated function  $Q(\boldsymbol{\psi}|\boldsymbol{\psi}^{(s)})$  for a generic iteration,  $s + 1$ , so the dependence on  $s$  will be suppressed. Similar to the case of GLMs, the M-step of the EM algorithm for GLMM can be computed by using IRLS of the form

$$\sum_{i=1}^n \frac{\int_{\mathbb{R}^q} c_i^{ls}(\mathbf{u}_i) p(\mathbf{u}_i) d\mathbf{u}_i}{\int_{\mathbb{R}^q} p(\mathbf{u}_i) d\mathbf{u}_i} \boldsymbol{\psi}^{(m+1)} = \sum_{i=1}^n \frac{\int_{\mathbb{R}^q} c_i^{rs}(\mathbf{u}_i) p(\mathbf{u}_i) d\mathbf{u}_i}{\int_{\mathbb{R}^q} p(\mathbf{u}_i) d\mathbf{u}_i}, \quad (2.19)$$

where

$$c_i^{ls}(\mathbf{u}_i) = \tilde{\mathbf{X}}_i \mathbf{W}_i^{(m)} \tilde{\mathbf{X}}_i^t, \quad \text{and} \quad c_i^{rs}(\mathbf{u}_i) = \tilde{\mathbf{X}}_i \mathbf{W}_i^{(m)} \mathbf{t}_i^{(m)}, \quad (2.20)$$

with

$$\tilde{\mathbf{X}}_i = \begin{pmatrix} \mathbf{X}_i \\ \boldsymbol{\xi}_i \end{pmatrix}_{(p+q^*) \times n_i} \quad (2.21)$$

and

$$\mathbf{t}_i^{(m)} = \tilde{\mathbf{X}}_i^T \boldsymbol{\psi}^{(m)} + \mathbf{g}'(\mu_i^{(m)}) \odot (\mathbf{y}_i - \mu_i^{(m)}), \quad \mathbf{W}_i^{(m)} = \text{diag} \left( w_{ij} b''(\theta_{ij}^{(m)}) \right)_{j=1}^{n_i}. \quad (2.22)$$

For each unobservable vector of random effects  $\mathbf{u}_i$ , SR rule expands the available data  $(\mathbf{y}, \mathbf{X}, \mathbf{Z})$  with the pseudo-data

$$\{\mathbf{u}_{im_1 m_2 m_3 kl}\} = \{\hat{\mathbf{u}}_i + r_{im_1 m_2} \mathbf{H}^{-1/2}(\hat{\mathbf{u}}_i) \mathbf{Q}_{im_1 m_2 m_3} \mathbf{V}_{kl}\} \quad (2.23)$$

and approximates (2.19) using sums weighted over the pseudo set (2.23). The SR approximation to (2.19) is therefore

$$\sum_{i=1}^n \frac{\mathfrak{d}_{1i}^{ls}}{\mathfrak{d}_{0i}} = \sum_{i=1}^n \frac{\mathfrak{d}_{1i}^{rs}}{\mathfrak{d}_{0i}}, \quad (2.24)$$

where

$$\mathfrak{d}_{1i}^\bullet = \sum_{m_1=1}^{M_1} \sum_{m_2=1}^{M_2} \gamma_{im_1 m_2} \left( \sum_{m_3=1}^{M_3} \sum_{k=1}^d \sum_{l=1}^{T_k} \nu_{kl} \mathcal{C}^\bullet(\mathbf{u}_{im_1 m_2 m_3 kl}) p(\mathbf{u}_{im_1 m_2 m_3 kl}) \right) \quad (2.25)$$

and

$$\mathfrak{d}_{0i} = \sum_{m_1=1}^{M_1} \sum_{m_2=1}^{M_2} \gamma_{im_1 m_2} \left( \sum_{m_3=1}^{M_3} \sum_{k=1}^d \sum_{l=1}^{T_k} \nu_{kl} p(\mathbf{u}_{im_1 m_2 m_3 kl}) \right). \quad (2.26)$$

Because we consider ratios of the integrals it is unnecessary to divide by the Monte Carlo sample sizes  $M_1$  and  $M_3$ . Recognizing that in the SR rule approximation the weights  $w_{ij}$ , the pseudo-covariates  $\mathbf{t}_i$ , as well as the expanded counterparts of  $\tilde{\mathbf{X}}_i$ , become random functions of the pseudo data (2.23), we denote

$$(\mathbf{X}_{SR})_{im_1 m_2 m_3 kl} = \tilde{\mathbf{X}}_i(\mathbf{u}_{im_1 m_2 m_3 kl}), \quad (\mathbf{t}_{SR})_{im_1 m_2 m_3 kl} = \mathbf{t}_i(\mathbf{u}_{im_1 m_2 m_3 kl}) \quad (2.27)$$

and

$$(\mathbf{W}_{SR})_{im_1m_2m_3kl} = \frac{1}{\mathfrak{d}_{0i}} \mathbf{W}_i(\mathbf{u}_{im_1m_2m_3kl}) p_{im_1m_2m_3kl} \gamma_{im_1m_2} \nu_{kl}. \quad (2.28)$$

Finally, with the notations above we get

$$\mathbf{X}_{SR} \mathbf{W}_{SR}^{(m)} \mathbf{X}_{SR}^T \boldsymbol{\psi}^{(m+1)} = \mathbf{X}_{SR} \mathbf{W}_{SR}^{(m)} \mathbf{t}_{SR}^{(m)} \quad (2.29)$$

where the matrix  $\mathbf{X}_{SR}$  is of size  $(p + q^*) \times NM_1M_2M_3T$ , the matrix  $\mathbf{W}_{SR}$  is a diagonal matrix of size  $NM_1M_2M_3T \times NM_1M_2M_3T$ , the vector  $\mathbf{t}_{SR}$  of size  $NM_1M_2M_3T \times 1$ ,  $N = n_1 + \dots + n_n$ , and  $T = T_1 + \dots + T_d$ .

### 2.1.5 Spherical rules and partial linearity of GLMMs

By combining radial approximations (2.10)-(2.12) with spherical ones (2.15)-(2.18), we can get twelve different spherical-radial rules. Following Genz and Monahan, we denote them as  $\text{SR}^{(l,m)}$ , where  $l$  corresponds to the order of the radial part and  $m$  is equal to that of the spherical rule. It is easy to see that by increasing MC size  $M_1$  the MC error of any  $\text{SR}^{(l,m)}$  rule can be made arbitrary small. Therefore, the question to be answered is which rule is the least computationally costly for a given MC error. Genz and Monahan [1999] conducted a simulation study where the performance of  $\text{SR}^{(1,1)}$ ,  $\text{SR}^{(3,3)}$ , and  $\text{SR}^{(5,5)}$  were compared given the same number of the integrand evaluations. Two different types of behavior of the integrand were considered, “close to linear” and “non-linear”. For “close to linear” case,  $\text{SR}^{(5,5)}$  exhibited the smallest approximation error among the three. For “nonlinear” case, both  $\text{SR}^{(3,3)}$  and  $\text{SR}^{(5,5)}$  showed a comparable approximation error with  $\text{SR}^{(1,1)}$  for  $q = 180$  and  $q = 360$  and performed somewhat better for  $q = 90$ . In addition, they demonstrated that the SR rules had a comparable accuracy with QMC methods for the integrands considered in Caflisch and Morokoff [1996] given similar numbers of integrand evaluations.

In this section, we will show how the cost of the evaluation of the integrands in (2.19) can be greatly reduced for higher order spherical rules (2.16)-(2.18). In particular, we use the fact that the cubature knots of (2.16)-(2.18) are highly structured, which allows us to recursively calculate the linear and bi-linear components of the integrands. Assuming the MC error of the GLMM integrals behaves similarly to those of Genz and Monahan [1999] higher order spherical rule should be the most effective. In our implementation of the SR approach, we choose to follow the spherical rules from Mysovskih [1981], where any knot can be presented as a linear combination of a few vectors from the standard basis  $\{\mathbf{e}_1, \dots, \mathbf{e}_q\}$ . This choice was determined by the fact that when we multiply a vector or a matrix by  $\mathbf{e}_t$  there is no need to perform an actual multiplication. The only operation which needs to be done is an extraction of the  $t$ th component of the vector or the  $t$ th column or row of the matrix. In other words, this saves us  $O(q)$  or  $O(q^2)$  flops for each operation. Genz and Monahan[1997,1998,1999 ] considered (2.15) and (2.16) as well as an alternative group of spherical rules based on the vertices of the standard simplex. However, the standard simplex spherical rules do not have the computational advantage of the standard basis spherical rules.

Let us start with the knots determining the third order rule (2.15). Let  $\delta_1 = 1$  and  $\delta_2 = -1$ . Then the first group of knots of (2.15) can be presented as

$$\{\mathbf{v}_{1l}\}_{l=1}^{T_1} = \{\delta_{s_1} \mathbf{e}_{t_1} : s_1 = 1, 2; t_1 = 1, \dots, q\}. \quad (2.30)$$

The other  $2q(q-1)$  knots can be written in terms of the standard basis as

$$\{\mathbf{v}_{2l}\}_{l=1}^{T_2} = \{1/\sqrt{2}(\delta_{s_1} \mathbf{e}_{t_1} + \delta_{s_2} \mathbf{e}_{t_2}) : s_1, s_2 = 1, 2; 1 = t_1 > t_2 = q\}. \quad (2.31)$$

Similar standard basis representations are available for the knots of the higher order spherical rules. In particular,

$$\{\mathbf{v}_{3l}\}_{l=1}^{T_3} = \begin{cases} 1/\sqrt{3}(\delta_{s_1} \mathbf{e}_{t_1} + \delta_{s_2} \mathbf{e}_{t_2} + \delta_{s_3} \mathbf{e}_{t_3}) \\ s_1, s_2, s_3 = 1, 2 \\ 1 = t_1 > t_2 > t_3 = q \end{cases} \quad (2.32)$$

and

$$\{\mathbf{v}_{4l}\}_{l=1}^{T_4} = \begin{cases} 1/2(\delta_{s_1}\mathbf{e}_{t_1} + \delta_{s_2}\mathbf{e}_{t_2} + \delta_{s_3}\mathbf{e}_{t_3} + \delta_{s_4}\mathbf{e}_{t_4}) \\ s_1, s_2, s_3, s_4 = 1, 2 \\ 1 = t_1 > t_2 > t_3 > t_4 = q. \end{cases} \quad (2.33)$$

Notice that the knots  $\{\mathbf{v}_{2l}\}_{l=1}^{T_2}$  from (2.18) do not follow (2.31), but can still be represented as linear combinations of two basis vectors. Therefore, the argument to follow is valid for them as well.

Using the structures of the knots (2.31)-(2.33), we get the following reductions in the complexity of some common matrix-vector operations:

$$\left[ \begin{array}{lll} (i) & \mathbf{v}_{ml_1}^T \mathbf{A} \mathbf{v}_{ml_2} & : O(q^2) \rightarrow O(m^2), \quad m = 2, 3, 4. \\ (ii) & \sum_{l=1}^{T_m} \mathbf{v}_{ml}^T \mathbf{A} \rho_l \mathbf{v}_{ml} & : O(q^2 T_m) \rightarrow O(m^2 T_m), \quad m = 2, 3, 4. \\ (iii) & \sum_{l=1}^{T_m} \rho_l \mathbf{v}_{ml} \mathbf{v}_{ml}^T & : O(q^2 T_m) \rightarrow O(m^2 T_m), \quad m = 2, 3, 4. \\ (iv) & \mathbf{A} \mathbf{v}_{ml} & : O(q^2) \rightarrow O(mq), \quad m = 2, 3, 4. \\ (v) & \sum_{l=1}^{T_m} \mathbf{A} \rho_l \mathbf{v}_{ml} & : O(q T_m) \rightarrow O(m T_m), \quad m = 2, 3, 4. \\ (vi) & \mathbf{a}^T \mathbf{v}_{ml} & : O(q) \rightarrow O(m), \quad m = 2, 3, 4. \end{array} \right. \quad (2.34)$$

where  $\{\rho_1, \dots, \rho_{T_m}\}$  is a set of scalars, the vector  $\mathbf{a}$  and the matrix  $\mathbf{A}$  do not depend on the sub-index  $l$ , and  $m$  is the order of the spherical rule.

Now let us identify the components of the IRLS algorithm (2.29) calculation that can be simplified according to (2.34). Calculating the pseudo data set (2.23) requires us to compute (iv) with  $\mathbf{A} = r_{im_1 m_2} \mathbf{H}^{-1/2}(\hat{\mathbf{u}}_i) \mathbf{Q}_{im_1 m_2 m_3}$ . An alternative to calculating actual  $\mathbf{u}_{im_1 m_2 m_3 kl}$ 's from the pseudo data set is to calculate the MC invariants with respect to the iterations of the IRLS. Calculating the linear predictor  $\theta_{ij}(\mathbf{u}_{im_1 m_2 m_3 kl})$  requires us to either compute (vi) at each iteration of the IRLS with  $\mathbf{a} = \mathbf{z}_{ij} \mathbf{D} r_{im_1 m_2} \mathbf{H}^{-1/2}(\hat{\mathbf{u}}_i) \mathbf{Q}_{im_1 m_2 m_3}$ , or (iv) with  $\mathbf{A} = \mathbf{P}(\mathbf{z}_{ij}) r_{im_1 m_2} \mathbf{H}^{-1/2}(\hat{\mathbf{u}}_i) \mathbf{Q}_{im_1 m_2 m_3}$ , keeping the results in memory. For  $p(\mathbf{u}_{im_1 m_2 m_3 kl})$  we calculate  $\mathbf{u}_{im_1 m_2 m_3 kl}^T \mathbf{u}_{im_1 m_2 m_3 kl}$ ,

which leads to (i) with  $\mathbf{A} = \mathbf{Q}_{im_1m_2m_3}^T \mathbf{H}^{-1}(\hat{\mathbf{u}}_i) \mathbf{Q}_{im_1m_2m_3}$ . Let us consider the left hand side of (2.29). There is (iii) with  $\rho_l = (\mathbf{W}_{SR})_l$  and (v) with  $\mathbf{A} = r_{im_1m_2} \mathbf{H}^{-1/2}(\hat{\mathbf{u}}_i)^T \mathbf{Q}_{im_1m_2m_3} \mathbf{P}(\mathbf{z}_{ij})$  and  $\rho_l = (\mathbf{W}_{SR})_l$ . For the right-hand side of (2.29), we compute (v) with  $\mathbf{A} = r_{im_1m_2} \mathbf{H}^{-1/2}(\hat{\mathbf{u}}_i)^T \mathbf{Q}_{im_1m_2m_3} \mathbf{P}(\mathbf{z}_{ij})$  and  $\rho_l = (\mathbf{W}_{SR})_l (\mathbf{t}_{SR})_l$ . So as we can see that representations (2.31)- (2.33) allow us to greatly reduce the computational complexity of the IRLS algorithm.

## 2.2 EM-LA<sub>2</sub>

The approach we will describe in this section, EM-LA<sub>2</sub>, is based on higher-order Laplace approximation of the integrals involved at the E-step of the EM algorithm. We will find a closed form of the standardized cumulants for GLMs which are the higher-order terms of the Laplace approximation. We then incorporate these into the EM algorithm. The illustrative examples will be considered in the next section.

Suppose function  $h(\mathbf{u})$  is a  $\mathcal{C}^6(\mathbb{R}^q)$  convex function with the global minimum at  $\hat{\mathbf{u}}$ . Suppose that the  $\mathcal{C}^5(\mathbb{R}^q)$  function  $\zeta(\mathbf{u})$  is such that  $|\zeta_{t_1 t_2 t_3 t_4}(\mathbf{u})| \leq C_1 \exp(C_2 |\mathbf{u}|^2)$ ,  $\forall \mathbf{u} \in \mathbb{R}^q$ , for some constants  $C_1$  and  $C_2$  and all fourth degree partial derivatives  $\zeta_{t_1 t_2 t_3 t_4}(\mathbf{u})$ . Then due to Kolassa [2006, Section 6.5], as well as personal communication with John Kolassa correcting the original formula, we have

$$\int_{\mathbb{R}^q} e^{-mh(\mathbf{u})} \zeta(\mathbf{u}) d\mathbf{u} = \frac{(2\pi)^{q/2} e^{-mh(\hat{\mathbf{u}})}}{\sqrt{\mathbf{det}[mh''(\hat{\mathbf{u}})]}} \left( \zeta(\hat{\mathbf{u}}) \frac{(1 + \tau_1)}{m} + \frac{\tau_2}{m} + O(m^{-2}) \right), \quad (2.35)$$

where  $\tau_1$  and  $\tau_2$  are defined below. The correction term  $\tau_1$  carries information about higher-order derivatives of the function  $h(\mathbf{u})$  and is given by

$$\tau_1 = -\frac{1}{8} \hat{\kappa}_4 + \frac{1}{24} (2\hat{\kappa}_{23}^2 + 3\hat{\kappa}_{13}^2) \quad (2.36)$$

where the standardized cumulants  $\hat{\kappa}_4$ ,  $\hat{\kappa}_{13}$ ,  $\hat{\kappa}_{23}$  are given by

$$\hat{\kappa}_4 = \sum_{t_1, t_2, t_3, t_4} \hat{h}_{t_1 t_2 t_3 t_4} \hat{h}^{t_1 t_2} \hat{h}^{t_3 t_4},$$

$$\hat{\kappa}_{13}^2 = \sum_{t_1, t_2, t_3, t_4, t_5, t_6} \hat{h}_{t_1 t_2 t_3} \hat{h}_{t_4 t_5 t_6} \hat{h}^{t_1 t_2} \hat{h}^{t_3 t_4} \hat{h}^{t_5 t_6},$$

and

$$\hat{\kappa}_{23}^2 = \sum_{t_1, t_2, t_3, t_4, t_5, t_6} \hat{h}_{t_1 t_2 t_3} \hat{h}_{t_4 t_5 t_6} \hat{h}^{t_1 t_4} \hat{h}^{t_2 t_5} \hat{h}^{t_3 t_6},$$

with

$$\hat{h}^{t_1 t_2} = [h''(\hat{\mathbf{u}})]_{t_1 t_2}^{-1}, \quad \hat{h}_{t_1 t_2 t_3} = \frac{\partial^3 h(\hat{\mathbf{u}})}{\partial u_{t_1} \partial u_{t_2} \partial u_{t_3}}, \quad \text{and} \quad \hat{h}_{t_1 t_2 t_3 t_4} = \frac{\partial^4 h(\hat{\mathbf{u}})}{\partial u_{t_1} \partial u_{t_2} \partial u_{t_3} \partial u_{t_4}}.$$

The correction term  $\tau_2$  contains information about an interaction of the first two derivatives of  $\zeta(\mathbf{u})$  with the third and fourth derivatives of  $h(\mathbf{u})$ , correspondingly. It is given by

$$\tau_2 = -\frac{1}{2} \sum_{t_1, t_2, t_3, t_4} \hat{\zeta}^{t_1} \hat{h}^{t_2 t_3 t_4} \hat{h}_{t_1 t_2} \hat{h}_{t_3 t_4} + \frac{1}{2} \sum_{t_1, t_2} \hat{\zeta}^{t_1 t_2} \hat{h}_{t_1 t_2}, \quad (2.37)$$

where

$$\hat{\zeta}^{t_1} = \frac{\partial \zeta(\hat{\mathbf{u}})}{\partial u_{t_1}} \quad \text{and} \quad \hat{\zeta}^{t_1 t_2} = \frac{\partial^2 \zeta(\hat{\mathbf{u}})}{\partial u_{t_1} \partial u_{t_2}}.$$

For notational convenience, let

$$\tau_{21} = \sum_{t_1, t_2, t_3, t_4} \hat{\zeta}^{t_1} \hat{h}^{t_2 t_3 t_4} \hat{h}_{t_1 t_2} \hat{h}_{t_3 t_4} \quad (2.38)$$

and

$$\tau_{22} = \sum_{t_1, t_2} \hat{\zeta}^{t_1 t_2} \hat{h}_{t_1 t_2}. \quad (2.39)$$

Then

$$\tau_2 = -\frac{1}{2} \tau_{21} + \frac{1}{2} \tau_{22}. \quad (2.40)$$

Now let us consider the  $i$ th term of the  $Q$ -function

$$E \left[ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}) | \mathbf{y}_i; \boldsymbol{\psi}^{(s)} \right] = \frac{\int_{\mathbb{R}^q} a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}) \exp \left\{ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)}) - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i \right\} d\mathbf{u}_i}{\int_{\mathbb{R}^q} \exp \left\{ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)}) - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i \right\} d\mathbf{u}_i}, \quad (2.41)$$

where  $a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}) = \sum_{j=1}^{n_i} w_{ij} [\theta_{ij} y_{ij} - b(\theta_{ij})]$ .

Applying (2.35) with

$$h(\mathbf{u}_i; \boldsymbol{\psi}^{(s)}) = \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i - a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)}) \quad (2.42)$$

and

$$\zeta(\mathbf{u}_i; \boldsymbol{\psi}) = a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}) \quad (2.43)$$

to both integrals in (2.41), we get

$$\tilde{E} \left[ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}) | \mathbf{y}_i; \boldsymbol{\psi}^{(s)} \right]_{LA_2} = \zeta(\hat{\mathbf{u}}_i, \boldsymbol{\psi}) + \frac{\tau_2(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)})}{1 + \tau_1(\hat{\mathbf{u}}_i, \boldsymbol{\psi}^{(s)})}. \quad (2.44)$$

Therefore, the  $LA_2$  approximation of the  $Q$  function is given by

$$\tilde{Q}(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)}) = \sum_{i=1}^n \left( \zeta(\hat{\mathbf{u}}_i, \boldsymbol{\psi}) + \frac{\tau_2(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)})}{1 + \tau_1(\hat{\mathbf{u}}_i, \boldsymbol{\psi}^{(s)})} \right). \quad (2.45)$$

Maximization of the  $\tilde{Q}(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)})$  at step  $s$  can be done using Newton-Raphson algorithm

$$\boldsymbol{\psi}^{(k+1)} = \boldsymbol{\psi}^{(k)} - [\tilde{Q}''_{\boldsymbol{\psi}\boldsymbol{\psi}}(\boldsymbol{\psi}^{(k)} | \boldsymbol{\psi}^{(s)})]^{-1} \tilde{Q}'_{\boldsymbol{\psi}}(\boldsymbol{\psi}^{(k)} | \boldsymbol{\psi}^{(s)}). \quad (2.46)$$

Below we will find all the components involved in

$$\tilde{Q}'_{\boldsymbol{\psi}}(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)}) = \sum_{i=1}^n \left( \zeta'_{\boldsymbol{\psi}}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}) + \frac{(\tau_2)'_{\boldsymbol{\psi}}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)})}{1 + \tau_1(\hat{\mathbf{u}}_i, \boldsymbol{\psi}^{(s)})} \right) \quad (2.47)$$

and

$$\tilde{Q}''_{\boldsymbol{\psi}\boldsymbol{\psi}}(\boldsymbol{\psi} | \boldsymbol{\psi}^{(s)}) = \sum_{i=1}^n \left( \zeta''_{\boldsymbol{\psi}\boldsymbol{\psi}}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}) + \frac{(\tau_2)''_{\boldsymbol{\psi}\boldsymbol{\psi}}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)})}{1 + \tau_1(\hat{\mathbf{u}}_i, \boldsymbol{\psi}^{(s)})} \right). \quad (2.48)$$



First, let us start with  $\tau_1(\hat{\mathbf{u}}_i, \boldsymbol{\psi}^{(s)})$  defined in (2.36). For notational convenience, we will omit super-index  $s$  while dealing with  $h(\mathbf{u}_i)$  below. The first four derivatives of the function

$$h(\mathbf{u}_i) = - \left( \sum_{j=1}^{n_i} \{w_{ij}[y_{ij}\theta_{ij} - b(\theta_{ij})] + c(y_{ij})\} - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i \right)$$

are

$$h'(\mathbf{u}_i) = \mathbf{u}_i - \mathbf{D}^T \sum_{j=1}^{n_i} w_{ij} [y_{ij} - b'(\theta_{ij})] \mathbf{z}_{ij} \quad (2.49)$$

$$h''(\mathbf{u}_i) = \mathbf{I}_q + \mathbf{D}^T \left( \sum_{j=1}^{n_i} w_{ij} b''(\theta_{ij}) \mathbf{z}_{ij} \mathbf{z}_{ij}^T \right) \mathbf{D} \quad (2.50)$$

$$h^{(3)}(\mathbf{u}_i) = \sum_{j=1}^{n_i} w_{ij} b^{(3)}(\theta_{ij}) \mathbf{D}^T \mathbf{z}_{ij} \mathbf{z}_{ij}^T \mathbf{D} \otimes \mathbf{D}^T \mathbf{z}_{ij} \quad (2.51)$$

$$h^{(4)}(\mathbf{u}_i) = \sum_{j=1}^{n_i} w_{ij} b^{(4)}(\theta_{ij}) \mathbf{D}^T \mathbf{z}_{ij} \mathbf{z}_{ij}^T \mathbf{D} \otimes \mathbf{D}^T \mathbf{z}_{ij} \mathbf{z}_{ij}^T \mathbf{D}. \quad (2.52)$$

If we denote

$$\gamma_{j_1 j_2} = \mathbf{z}_{ij_1}^T \mathbf{D} [\hat{h}'']^{-1} \mathbf{D}^T \mathbf{z}_{ij_2}, \quad j_1, j_2 \in \{1, \dots, n_i\} \quad (2.53)$$

then, similarly to the correction terms of the saddlepoint approximation of the GLM in Section 3.3, it can be shown that

$$\hat{\kappa}_4 = \sum_{j=1}^{n_i} w_{ij} b^{(4)}(\hat{\theta}_{ij}) \gamma_{jj}^2, \quad \hat{\kappa}_{13}^2 = \sum_{j_1=1}^{n_i} \sum_{j_2=1}^{n_i} w_{ij_1} w_{ij_2} b^{(3)}(\hat{\theta}_{ij_1}) b^{(3)}(\hat{\theta}_{ij_2}) \gamma_{j_1 j_1} \gamma_{j_1 j_2} \gamma_{j_2 j_2}.$$

and

$$\hat{\kappa}_{23}^2 = \sum_{j_1=1}^{n_i} \sum_{j_2=1}^{n_i} w_{ij_1} w_{ij_2} b^{(3)}(\hat{\theta}_{ij_1}) b^{(3)}(\hat{\theta}_{ij_2}) \gamma_{j_1 j_2}^3.$$

Now we need to find the first and the second derivatives of  $\zeta(\hat{\mathbf{u}}_i, \boldsymbol{\psi})$  and  $\tau_2(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)})$  with respect to  $\boldsymbol{\psi}$ . For the function

$$\zeta(\hat{\mathbf{u}}_i, \boldsymbol{\psi}) = \sum_{j=1}^{n_i} w_{ij} [y_{ij} \theta_{ij} - b(\theta_{ij})],$$

the first derivative is given by

$$\zeta'_{\boldsymbol{\psi}}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}) = \sum_{j=1}^{n_i} w_{ij} [y_{ij} - b'(\theta_{ij})] \hat{\mathbf{x}}_{ij}$$

and the second derivative is therefore

$$\zeta''_{\boldsymbol{\psi}\boldsymbol{\psi}}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}) = - \sum_{j=1}^{n_i} w_{ij} b''(\theta_{ij}) \hat{\mathbf{x}}_{ij} \hat{\mathbf{x}}_{ij}^T.$$

To find the derivatives of  $\tau_2(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)})$ , we need to find those of  $\tau_{21}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)})$  and  $\tau_{22}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)})$ . Using the same argument as in Section 3.3, it can be shown that

$$\tau_{22}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)}) = - \sum_{j=1}^{n_i} w_{ij} b''(\theta_{ij}) \gamma_{jj}(\boldsymbol{\psi}, \boldsymbol{\psi}^{(s)}) \quad (2.54)$$

and

$$\tau_{21}(\hat{\mathbf{u}}_i, \boldsymbol{\psi}, \boldsymbol{\psi}^{(s)}) = \sum_{j=1}^{n_i} w_{ij} [y_{ij} - b'(\theta_{ij})] \gamma_{j\cdot}(\boldsymbol{\psi}, \boldsymbol{\psi}^{(s)}), \quad (2.55)$$

where

$$\gamma_{jj}(\boldsymbol{\psi}, \boldsymbol{\psi}^{(s)}) = \boldsymbol{\sigma}^T \mathbf{P}(\mathbf{z}_{ij}) [\hat{h}^{(s)''}]^{-1} \mathbf{P}^T(\mathbf{z}_{ij}) \boldsymbol{\sigma}, \quad j \in \{1, \dots, n_i\}, \quad (2.56)$$

with  $\hat{h}''$  given by (2.49) and evaluated at  $\boldsymbol{\psi}^{(s)}$  and

$$\gamma_{j\cdot}(\boldsymbol{\psi}, \boldsymbol{\psi}^{(s)}) = \boldsymbol{\sigma}^T \mathbf{P}(\mathbf{z}_{ij}) [\hat{h}'']^{-1} \boldsymbol{\Gamma}^{(s)}, \quad j \in \{1, \dots, n_i\},$$

where

$$\boldsymbol{\Gamma}^{(s)} = \sum_{j_2=1}^{n_i} w_{ij_2} b^{(3)}(\theta_{ij_2}^{(s)}) \gamma_{j_2 j_2}^{(s)} \mathbf{P}(\mathbf{z}_{ij_2})^T \boldsymbol{\sigma}^{(s)}.$$

Omitting the dependence on  $\hat{\mathbf{u}}_i$  and  $\boldsymbol{\psi}^{(s)}$ , the first derivatives are given by

$$(\tau_{22})'_{\boldsymbol{\psi}}(\boldsymbol{\psi}) = - \sum_{j=1}^{n_i} w_{ij} b^{(3)}(\theta_{ij}) \gamma_{jj}(\boldsymbol{\psi}) \hat{\mathbf{x}}_{ij} - \sum_{j=1}^{n_i} w_{ij} b''(\theta_{ij}) [\gamma_{jj}(\boldsymbol{\psi})]'_{\boldsymbol{\psi}} \quad (2.57)$$

and

$$(\tau_{21})'_{\boldsymbol{\psi}}(\boldsymbol{\psi}) = - \sum_{j=1}^{n_i} w_{ij} b''(\theta_{ij}) \gamma_{j\cdot}(\boldsymbol{\psi}) \hat{\mathbf{x}}_{ij} + \sum_{j=1}^{n_i} w_{ij} [y_{ij} - b'(\theta_{ij})] [\gamma_{j\cdot}(\boldsymbol{\psi})]'_{\boldsymbol{\psi}}, \quad (2.58)$$

with

$$[\gamma_{jj}(\boldsymbol{\psi})]'_{\boldsymbol{\psi}} = \begin{bmatrix} \mathbf{0}_{p \times 1} \\ 2\mathbf{P}(\mathbf{z}_{ij})[\hat{h}'' ]^{-1}\mathbf{P}^T(\mathbf{z}_{ij})\boldsymbol{\sigma} \end{bmatrix}$$

and

$$[\gamma_{j\cdot}(\boldsymbol{\psi})]'_{\boldsymbol{\psi}} = \begin{bmatrix} \mathbf{0}_{p \times 1} \\ \mathbf{P}(\mathbf{z}_{ij})[\hat{h}'' ]^{-1}\boldsymbol{\Gamma}^{(s)} \end{bmatrix}.$$

The second derivatives are therefore

$$\begin{aligned} (\tau_{22})''_{\boldsymbol{\psi}\boldsymbol{\psi}}(\boldsymbol{\psi}) &= - \sum_{j=1}^{n_i} w_{ij}b^{(4)}(\theta_{ij})\gamma_{jj}(\boldsymbol{\psi})\hat{\mathbf{x}}_{ij}\hat{\mathbf{x}}_{ij}^T - 2 \sum_{j=1}^{n_i} w_{ij}b^{(3)}(\theta_{ij})[\gamma_{jj}(\boldsymbol{\psi})]'_{\boldsymbol{\psi}}\hat{\mathbf{x}}_{ij}^T \\ &\quad - \sum_{j=1}^{n_i} w_{ij}b^{(2)}(\theta_{ij})[\gamma_{jj}(\boldsymbol{\psi})]''_{\boldsymbol{\psi}\boldsymbol{\psi}} \end{aligned}$$

and

$$(\tau_{21})''_{\boldsymbol{\psi}\boldsymbol{\psi}}(\boldsymbol{\psi}) = - \sum_{j=1}^{n_i} w_{ij}b^{(3)}(\theta_{ij})\gamma_{j\cdot}(\boldsymbol{\psi})\hat{\mathbf{x}}_{ij}\hat{\mathbf{x}}_{ij}^T - 2 \sum_{j=1}^{n_i} w_{ij}b''(\theta_{ij})[\gamma_{j\cdot}(\boldsymbol{\psi})]'_{\boldsymbol{\psi}}\hat{\mathbf{x}}_{ij}^T$$

with

$$[\gamma_{jj}(\boldsymbol{\psi})]''_{\boldsymbol{\psi}\boldsymbol{\psi}} = \begin{bmatrix} \mathbf{0}_{p \times p} & \mathbf{0}_{p \times q^*} \\ \mathbf{0}_{q^* \times p} & 2\mathbf{P}(\mathbf{z}_{ij})[\hat{h}'' ]^{-1}\mathbf{P}^T(\mathbf{z}_{ij}) \end{bmatrix}.$$

This completes the construction of the NR algorithm (2.46). Notice that in this case we cannot rewrite the NR algorithm in a form similar to IRLS due to the additional contribution from the terms  $\gamma_{jj}(\boldsymbol{\psi})$  and  $\gamma_{j\cdot}(\boldsymbol{\psi})$ .

## 2.3 Examples

For the two examples considered in this section we set  $\alpha = \beta = \gamma_1 = \gamma_2 = 0.05$  and  $\delta_1 = 0.001$  and  $\delta_2 = 0.005$ ,  $k = 5$  for the ascent-based stopping rule.

### 2.3.1 Minnesota Health Plan Data

First we present results for the Minnesota Health Plan data [Waller and Zelterman, 1997], and the Poisson linear mixed model described in Section 1.3.2. A similar model was proposed by Booth et al. [2003] for this data, the difference being that the event by period interaction term was not included in their analysis. Table 2.1 gives the ML estimates and their standard errors. We started the algorithm with  $M_1 = 20$ . Convergence was declared after 69 iterations with  $M_1^{(69)} = 820$  and  $M_1^{max} = 1370$ . The current implementation of the  $SR^{(3,5)}$  provides approximately two-fold gain in the speed compared to  $SR^{(3,3)}$  and gives the similar estimates. We are currently working on the implementation of the higher order spherical rules utilizing (2.31)-(2.33), which should provide an even faster convergence. For comparison, we fit the same model using the SAS/GLIMMIX [SAS, 2005] procedure (see Appendix), which employs a restricted pseudo-likelihood method by default. The other estimates reported were obtained by using the Bayesian software package WinBUGS [D.J.Spiegelhalter et al., 1999]. The values given for WinBUGS are medians and standard deviations of the marginal posterior distributions obtained using the weakly-informative priors  $a_0, a_1, b_1, b_2, b_3, c_{11}, c_{12}, c_{13} \sim N(0, 10^6)$  and  $1/\sigma_\gamma^2, 1/\sigma_\nu^2, 1/\sigma_\omega^2 \sim U[0, 10^3]$ . As we can see, the estimates of all parameters except that of the constant agree. The MCEM-SR estimate of  $a_0$  is close to that of WinBUGS. Also, based on the ML estimates and their standard errors, it appears that there is a significant event by period interaction. EM-LA<sub>2</sub> was quite robust to a starting value. It performed really well for this example and gave highly accurate estimators. Although, it seems to underestimate  $\sigma_\gamma$  parameter. To compare our results to those of Booth et al. [2003] we refit the model without the interaction term. Table 2.2 gives the results for this model. In this case the MCEM-SR<sup>(3,3)</sup> algorithm converged at the 76th iteration with  $M_1^{(76)} = 720$  and  $M_1^{max} = 1130$ . Our results are in agreement with the estimates obtained using WinBUGS and the SAS/GLIMMIX

Table 2.1: Parameter estimates for the Poisson linear mixed effects model (1.27) obtained by maximum likelihood and using the SAS/GLIMMIX and WinBUGS software packages and using EM-LA<sub>2</sub>.

	With Interaction			
	MCEM-SR	GLIMMIX	WinBUGS	EM-LA <sub>2</sub>
$a_0$	0.868 (0.096)	0.961 (0.104)	0.844 (0.109)	0.856
$a_1$	-0.165 (0.127)	-0.164 (0.106)	-0.160 (0.110)	-0.169
$b_1$	-0.091 (0.095)	-0.089 (0.109)	-0.085 (0.111)	-0.090
$b_2$	0.414 (0.098)	0.394 (0.104)	0.422 (0.110)	0.415
$b_3$	0.491 (0.109)	0.468 (0.103)	0.498 (0.110)	0.493
$c_{11}$	0.246 (0.097)	0.240 (0.103)	0.243 (0.103)	0.246
$c_{12}$	0.104 (0.080)	0.101 (0.095)	0.102 (0.097)	0.104
$c_{13}$	-0.085 (0.099)	-0.084 (0.096)	-0.088 (0.097)	-0.085
$\sigma_\gamma$	0.493 (0.082)	0.491 (0.081)	0.511 (0.078)	0.526
$\sigma_\nu$	0.608 (0.056)	0.578 (0.048)	0.605 (0.053)	0.601
$\sigma_\omega$	0.625 (0.040)	0.593 (0.034)	0.627 (0.038)	0.628

procedures. However, the estimates reported by Booth et al. [2003] appear to be incorrect. EM-LA<sub>2</sub> again shows very good performance.

### 2.3.2 Salamander Mating Data

The salamander data from McCullagh and Nelder [1989, pages 439-450] have been analyzed by numerous authors using linear mixed effects models for binary responses [Karim and Zeger, 1992, McCulloch, 1994, Lee and Nelder, 1996, Booth and Hobert, 1999, Sung and Geyer, 2006]. Here we consider the logit-normal GLMM described by

Table 2.2: Parameter estimates for the Poisson linear mixed effects model (1.27) obtained by maximum likelihood and using the SAS/GLIMMIX and WinBUGS software packages and using EM-LA<sub>2</sub>.

Without Interaction					
	MCEM-SR	GLIMMIX	WinBUGS	BCFH	EM-LA <sub>2</sub>
$a_0$	0.763 (0.109)	0.854 (0.099)	0.744 (0.107)	1.64 (0.001)	0.742
$a_2$	0.109 (0.109)	0.110 (0.083)	0.111 (0.087)	-0.12 (0.001)	0.108
$b_2$	0.435 (0.108)	0.414 (0.093)	0.481 (0.176)	0.35 (0.001)	0.435
$b_3$	0.425 (0.106)	0.402 (0.093)	0.470 (0.176)	0.23 (0.001)	0.425
$b_4$	-0.028 (0.904)	-0.026 (0.096)	-0.021 (0.102)	0.17 (0.001)	-0.028
$\sigma_\gamma$	0.499 (0.084)	0.493 (0.080)	0.510 (0.082)	1.04 (0.091)	0.535
$\sigma_\nu$	0.604 (0.059)	0.574 (0.048)	0.598 (0.052)	0.60 (0.053)	0.596
$\sigma_\omega$	0.623 (0.043)	0.591 (0.034)	0.624 (0.038)	0.60 (0.036)	-0.625

Booth and Hobert [1999], which is a frequentist version of the Bayesian model proposed by Karim and Zeger [1992]. As noted by Booth and Hobert [1999], Sung and Geyer [2006], and others, maximum likelihood estimation for this model is quite challenging.

The data, as described in McCullagh and Nelder [1989], arise from three experiments, each involving two groups consisting of twenty salamanders, 10 Roughbutt (R) and 10 Whiteside (W), with 5 males and 5 females in each case. Thus, there are 100 possible heterosexual crosses in each group. However, due to time constraints, only 60 crosses were permitted in each group. Two of the experiments involved the same set of 40 salamanders. However, following McCullagh and Nelder [1989, page 441] and Booth and Hobert [1999, Section 7.3] we shall analyze the study as though it consisted of 6 independent groups of 20 salamanders, each resulting in 60 binary indicators of successful mating.

Let  $\pi_{ij}$  denote the probability of successful mating for pair  $j$  in group  $i$ ,  $j = 1, \dots, 60$ ,  $i = 1, \dots, 6$ . Let  $\mathbf{u}_i^f$  and  $\mathbf{u}_i^m$  denote random effect vectors associated with the 10 female and 10 male salamanders in group  $i$ , and suppose that  $(\mathbf{u}_i^{fT}, \mathbf{u}_i^{mT})^T \sim \mathbf{D}\mathbf{u}_i$ , where  $\mathbf{u}_i \sim N_{20}(\mathbf{0}, \mathbf{I})$ , and

$$\mathbf{D} = \begin{pmatrix} \sigma_f \mathbf{I}_{10} & \mathbf{0}_{10} \\ \mathbf{0}_{10} & \sigma_m \mathbf{I}_{10} \end{pmatrix}$$

Booth and Hobert [1999] consider a logit model of the form

$$\log \left( \frac{\pi_{ij}}{1 - \pi_{ij}} \right) = \mathbf{x}_{ij}^T \boldsymbol{\beta} + \mathbf{z}_{ij}^T \mathbf{D}\mathbf{u}_i, \quad (2.59)$$

where  $\mathbf{x}_{ij}$  is a  $4 \times 1$  vector indicating the type of cross, and  $\mathbf{z}_{ij}$  is a  $20 \times 1$  vector with 1's at the coordinates corresponding to pair  $j$ , and 0's otherwise. The parameter vector

$$\boldsymbol{\beta} = (\boldsymbol{\beta}_{R/R}, \boldsymbol{\beta}_{R/W}, \boldsymbol{\beta}_{W/R}, \boldsymbol{\beta}_{W/W})^T$$

consists of unknown fixed coefficients associated with the four types of cross, with subscripts indicating the species of the female and male respectively.

The likelihood in this example involves six intractable 20-dimensional integrals. Maximum likelihood estimates of the parameter vector  $\boldsymbol{\psi} = (\boldsymbol{\beta}^T, \boldsymbol{\sigma}^T)^T$  obtained using the MCEM-SR<sup>(3,3)</sup> algorithm are displayed in Table 2.3. To compare our results with those of Booth and Hobert [1999] we started with  $\theta^{(0)} = (0, 0, 0, 0, 1, 1)$ . The algorithm converged after 48 iterations, with  $M_1^{(48)} = 365$  and  $M_1^{max} = 840$ . The current implementation of MCEM-SR<sup>(3,5)</sup> took on average three times less time than MCEM-SR<sup>(3,3)</sup>. Again, the implementation of the higher order spherical rules utilizing (2.31)-(2.33) as well as the new implementation of MCEM-SR<sup>(3,5)</sup> are expected to provide an even faster convergence. The MCEM-SR estimates agree with the ones obtained by Booth and Hobert [1999], who used an MCEM algorithm involving importance sampling at the E-step. Booth and Hobert [1999] reported convergence in 51 iterations. Their Monte Carlo sample size increased from 1000 at the beginning

to 66,169 at the end of the MCEM algorithm. Hence, much less computational effort was required in MCEM-SR to reach the same level of accuracy. EM-LA<sub>2</sub> developed in section 2.2 can not be used for the model. The right form of higher-order correction in this setting needs to be found using a similar argument as in Shun and McCullagh [1995]. For completeness, we provide the EM-LA<sub>2</sub> estimates in Table 2.3. As we see they are extremely biased compared to those given by MCEM-SR and BH. In addition, Table 2.3 contains the Bayesian estimates based on non-informative priors of Karim and Zeger [1992] (KZ). Booth and Hobert [1999] also reported the estimates produced by SAS%GLIMMIX macro (GLIMMIX(BH)), which was not part of the SAS/STAT package at that time. We refitted the model using the current version of SAS/GLIMMIX with default settings that estimate models using restricted maximum pseudo-likelihood (GLIMMIX). Finally, we fitted the model running SAS/GLIMMIX (see Appendix) with the other available pseudo-likelihood estimation techniques (not reported here) such as MSPL, RMPL, and MMPL (see SAS [2005]). The results were far from ours and those of Booth and Hobert [1999]. Therefore, it appears that SAS/GLIMMIX cannot handle the estimation of a GLMM involving high-dimensional integrals as in the Salamander data case.

## 2.4 Discussion

In this chapter, we have proposed a computationally feasible MCEM algorithm for fitting a GLMM with multivariate normal random effects. Our MCEM-SR algorithm can be generalized to GLMMs with other symmetric random effects distributions such as the multivariate t-distribution. In addition, we described how partial linearity of GLMMs can be exploited to significantly reduce the computational cost of the approach.



Table 2.3: Maximum likelihood estimates for the logit-normal model (2.59) obtained using the the MCEM-SR algorithm along with their standard errors. Maximum likelihood estimates obtained by EM-LA<sub>2</sub>. Maximum likelihood estimates reported by Booth and Hobert [1999], and by Sung and Geyer [2006] (<http://www.stat.umn.edu/geyer/bernor/>), as well as posterior means obtained from a Bayesian analysis of the same model in Karim and Zeger [1992] are given for comparison.

	$\beta_{R/R}$	$\beta_{R/W}$	$\beta_{W/R}$	$\beta_{W/W}$	$\sigma_f$	$\sigma_m$
MCEM-SR	1.022 (0.224)	0.325 (0.241)	-1.944 (0.274)	0.999 (0.240)	1.180 (0.152)	1.116 (0.159)
EM-LA <sub>2</sub>	1.308	0.391	-2.51	1.25	2.25	2.15
BH	1.030	0.320	-1.950	0.990	1.183	1.118
SG	1.004 (0.161)	0.534 (0.271)	-1.783 (0.101)	1.268 (0.606)	1.099 (0.149)	1.167 (0.237)
KZ	1.03	0.34	-1.98	1.07	1.50	1.36
GLIMMIX	0.787 (0.320)	0.247 (0.311)	-1.500 (0.352)	0.777 (0.320)	0.848 (0.194)	0.797 (0.193)
GLIMMIX(BH)	0.87	0.28	-1.69	0.95	1.16	0.96

These results show that MCEM-SR performs very well both in terms of the accuracy of the estimates and the Monte Carlo sample size necessary to attain this accuracy. It should not be a surprise that we needed a Monte Carlo sample size of 1370 for Minnesota data with a 7-dimensional random effect, and only 840 for Salamander data involving a 20-dimensional random effect. The Monte Carlo sample size in MCEM-SR is determined not only by the dimension of the random effect, but also by the number of independent subjects observed. This follows from the fact that the variance of a MC approximation of a sum of  $n$   $q$ -dimensional integrals is proportional to  $n$ .

For another example of the accuracy of the SR rule, consider the following. In the salamander example, when we ran our algorithm with the Monte Carlo sample size  $M_1$  fixed at 2, MCEM converged to the MLE from Table 5 and then oscillated around it with a MC standard error of approximately 0.1. This is quite impressive considering the challenges reported by Sung and Geyer [2006] for this model.

The use of randomized spherical radial integration at the E-step of the EM algorithm leads to a computationally feasible algorithm for fitting GLMMs. We have illustrated the power of the method with some challenging examples. We are in the process of developing an R package to implement the described MCEM-SR algorithm.

In the second part of this chapter, we found a closed form of the standardized cumulants for GLMs which has not been recognized in the literature. Then using the fact that the standardized cumulants are the higher-order terms of the Laplace approximation, we developed EM-LA<sub>2</sub> approach. We applied the method to the Minnesota Health Plan Data. The estimates produced by EM-LA<sub>2</sub> were highly accurate showing the great potency of the approach. However, further research is needed to adapt the approach to binary data.

CHAPTER 3  
COUNTING TABLES USING THE DOUBLE SADDLEPOINT  
APPROXIMATION

### 3.1 Introduction

Determining the number of contingency tables with a given set of marginal totals is a well-known combinatorial problem. More generally, one can ask how many tables there are in a reference set determined by a collection of linear constraints. This problem is relevant in the context of exact conditional statistical tests based on loglinear models for contingency tables generated by multinomial sampling, and for conditional volume tests that assign equal probability to every table in the reference set. In this paper we propose a new analytical approximation which is accurate and easily computed in a wide range of problems and which can be used to determine whether such enumeration is feasible. A related approximation can be used to determine the number of tables of zeros and ones with fixed margins.

Let  $\{y_{ij}\}$  denote the counts in an  $r \times c$  contingency table. Gail and Mantel [1977] obtained the following approximation for the number of tables with the same margins via an application of the central limit theorem.

Let  $(Y_{i1}, \dots, Y_{ic})$  denote a random vector that assigns equal probability to every ordered set of  $c$  non-negative integers summing to  $y_{i\cdot}$ , independently for  $i = 1, \dots, r$ .

Then

$$\begin{aligned} E(Y_{ij}) &= y_{i\cdot}/c, \\ \text{var}(Y_{ij}) &= y_{i\cdot}(y_{i\cdot} + c)(c - 1)/(c + 1)c^2, \\ \text{cov}(Y_{ij}, Y_{ik}) &= -y_{i\cdot}(y_{i\cdot} + c)/(c + 1)c^2. \end{aligned}$$

It follows that the column sums,  $Y_{.1}, \dots, Y_{.c}$ , are identically distributed and equicorrelated with

$$\begin{aligned} E(Y_{.j}) &= y_{..}/c, \\ \sigma^2 = \text{var}(Y_{.j}) &= \sum_{i=1}^r y_{i.}(y_{i.} + c)(c - 1)/(c + 1)c^2, \\ \text{cov}(Y_{.j}, Y_{.k}) &= -\sigma^2/(c - 1). \end{aligned}$$

Hence, the multivariate normal approximation to the conditional probability of the observed vector of column marginal totals given the row totals is

$$p(\{y_{.j}\}) = ((c - 1)/2\pi\sigma^2c)^{(c-1)/2} c^{1/2} \exp(-Q/2),$$

where  $Q = ((c - 1)/\sigma^2c)(\sum_{j=1}^c y_{.j}^2 - y_{..}^2/c)$  and  $\{y_{.j}\} \equiv \{y_{.j} : 1 \leq j \leq c\}$ . The total number of tables with unrestricted column totals is

$$N(\{y_{i.}\}) = \prod_{i=1}^r \binom{y_{i.} + c - 1}{c - 1}. \quad (3.1)$$

The Gail and Mantel approximation to the number of tables with the same row and column margins as  $\{y_{ij}\}$  is then  $N(\{y_{i.}\}) \times p(\{y_{.j}\})$ .

As an example, Gail and Mantel consider the  $4 \times 3$  table with row and column margins  $\{20, 10, 5, 5\}$  and  $\{11, 10, 19\}$  respectively. In this case the approximation gives 21,469 tables, which is in good agreement with the exact number, 22,245. However, the approximation is not symmetric in the rows and columns. If the approximation is applied to the transpose of the contingency table the approximation to the number of tables is 11,933, which is far from the correct answer. To be fair, the approximation can be expected to work well when the number of rows (or columns) being averaged over is large relative to the number of columns (or rows), and so it is not surprising that the approximation based on averaging over rows is better in this instance. As another example, consider the  $5 \times 5$  table of pathologists ratings from Holmquist et al. [1967] [see also

Agresti, 1990, p.368]. In this case the row and column margins are  $\{26, 26, 38, 22, 6\}$ , and  $\{27, 12, 69, 7, 3\}$ , respectively. The normal approximation gives 12.5 billion tables, and 261 billion after transposing the rows and columns. The correct answer in this case is 193,316,293,000, which was computed using exact algebraic methods.

Another approach, based on an equivalence between bicolored graphs and matrices, was exploited by Békéssy et al. [1972] and leads to a different approximation for the number of two-way contingency tables with fixed row and column margins given by

$$N(\{y_{i.}\}, \{y_{.j}\}) \approx \frac{y_{..}! \exp(\alpha)}{\prod_{i=1}^r y_{i.}! \prod_{j=1}^c y_{.j}!}, \quad (3.2)$$

where

$$\alpha = \frac{2}{y_{..}^2} \cdot \sum_{i=1}^r \binom{y_{i.}}{2} \cdot \sum_{j=1}^c \binom{y_{.j}}{2}.$$

The same result was obtained in Good and Crook [1977] as a special case. Using an asymptotic argument Bender [1974] suggested a related approximation which makes an adjustment for zero elements of a two-way table. His approximation is given by

$$N(\{y_{i.}\}, \{y_{.j}\}) \approx \frac{y_{..}! \exp(\alpha_1 + \alpha^*)}{\prod_{i=1}^r y_{i.}! \prod_{j=1}^c y_{.j}!}, \quad (3.3)$$

where

$$\alpha_1 = \frac{1}{2y_{..}^2} \cdot \left( \sum_{i=1}^r y_{i.}^2 - y_{..} \right) \left( \sum_{j=1}^c y_{.j}^2 - y_{..} \right) \quad \text{and} \quad \alpha^* = \frac{1}{y_{..}} \sum_{(i,j):y_{ij}=0} y_{i.} y_{.j}.$$

Applying formulas (3.2) and (3.3) to the pathologists ratings table gives the values  $2.487 \times 10^{211}$  and  $7.283 \times 10^{200}$ , respectively, and so both approximations provide quite unsatisfactory estimates in this example. A better performance may be expected from the estimators for contingency tables with a large number of rows and columns.

Yet another analytical approximation for the number of two-way contingency tables with fixed margins is given in dia. However, this approximation can also be quite

inaccurate. Holmes and Jones [1996] give an example of a  $5 \times 4$  table with row margins,  $\{9, 49, 182, 478, 551\}$ , and column margins,  $\{9, 309, 355, 596\}$ . In this example the exact number of possible tables is 33,819,042,818,100,768 or  $3.382 \times 10^{16}$  to four significant figures. Applying the Diaconis-Efron formula results in the approximations,  $1.319 \times 10^{17}$ , and  $4.126 \times 10^{16}$ , after switching rows and columns. Thus, the Diaconis-Efron formula is in error by at least 20%.

In this chapter we propose a double-saddlepoint approximation to the number of contingency tables whose counts meet certain linear constraints. The approximation is based on a probabilistic formulation involving a geometric generalized linear model. Computing the approximation involves fitting the generalized linear model (GLM) which can be accomplished essentially instantaneously. The approximation is shown to be extremely accurate in a range of examples. The accuracy is best when the degrees of freedom of the GLM is large relative to the dimension of the sufficient statistic because, in this case, the sufficient statistics involve sums over a large number of cells. The approximation is less accurate when the degrees of freedom is small relative to the dimension of the sufficient statistic but, in such cases, the number of tables meeting the linear constraints tends to be small and can often be computed by other means. For example, the approximation to the number of tables with the pathologists ratings table margins is 205 billion. Transposing the table makes little difference resulting in a value of 202 billion. For the data from Gail and Mantel [1977] the corresponding approximations are 20,321 and 21,536, and for the data from Holmes and Jones [1996] the approximations are respectively  $3.303 \times 10^{16}$  and  $3.428 \times 10^{16}$ . However, in almost all cases the approximation is improved by using an easily computed higher-order correction to the double saddlepoint.

An outline of the chapter is as follows. In Section 3.2 we discuss the formulation

of the counting problem for two-way tables with fixed margins in terms of a geometric generalized linear model. The double saddlepoint approximation and higher-order correction are described in Section 3.3. The GLM formulation is then generalized to include multi-way tables and tables with additional constraints in Section 3.4. Results for several examples are presented in Section 3.5. A similar approximation for tables containing only zeros and ones based on a logistic GLM probabilistic formulation is presented in Section 3.6. Exact algebraic and importance sampling methods for table counting are discussed briefly in Section 3.7. The chapter concludes in Section 3.8 with some discussion.

## 3.2 GLM Formulation

Let  $Y$  be a geometric random variable with success probability,  $\pi$ . Then,  $\mu = E(Y) = (1 - \pi)/\pi$ , and for  $y = 0, 1, \dots$ ,

$$\begin{aligned} P(Y = y) &= (1 - \pi)^y \pi \\ &= \left( \frac{\mu}{\mu + 1} \right)^y \frac{1}{\mu + 1} \\ &= \exp \{ y\theta + \log(1 - e^\theta) \}, \end{aligned}$$

where  $\theta = \log(\mu) - \log(\mu + 1)$  is the canonical parameter. If  $Y_1, \dots, Y_c$  are i.i.d. geometric random variables, then their sum,  $Y.$ , is negative binomial with mass function,

$$P(Y. = y.) = \binom{y. + c - 1}{c - 1} (1 - \pi)^y \pi^c$$

for  $y. = 0, 1, \dots$ . It follows that the conditional distribution of  $(Y_1, \dots, Y_c)$  given  $Y. = y.$  is given by

$$P(Y_1 = y_1, \dots, Y_c = y_c | Y. = y.) = \left( \binom{y. + c - 1}{c - 1} \right)^{-1},$$

for all non-negative count vectors,  $(y_1, \dots, y_c)$ , summing to  $y$ .

Now, let  $\{Y_{ij}\}$  be a table of counts whose entries are independent geometric random variables with canonical parameters,  $\{\theta_{ij}\}$ . Consider the generalized linear model,

$$\theta_{ij} = \lambda + \lambda_i^R + \lambda_j^C \quad (3.4)$$

for  $i = 1, \dots, r$  and  $j = 1, \dots, c$ , where  $R$  and  $C$  denote the nominal-scale row and column factors. Notice that the row and column margins are sufficient statistics for this model. Hence, the conditional distribution of the table counts given the margins is the same regardless of the values of the parameters in the model. In particular, suppose that the column effects are all equal,  $\lambda_1^C = \dots = \lambda_c^C = 0$  say. In this case the counts in each row of the table are i.i.d.. Furthermore, after conditioning on a row margin, the probabilities of all ordered sets of counts summing to the margin are equal.

### 3.3 Double-Saddlepoint Approximation

The double-saddlepoint approximation provides an accurate alternative to the normal approximation which can be formulated in terms of the GLM described in the previous section. Specifically, let  $\mathbf{y}$  denote the vector of counts for a two-way table of length  $n = rc$ . Suppose that the counts are independent geometric random variables with canonical parameters given by (3.4). The loglikelihood for the parameter vector,  $\boldsymbol{\lambda}$ , has the form

$$\begin{aligned} l(\boldsymbol{\lambda}) &= \sum_{i=1}^n (y_i \mathbf{x}_i^T \boldsymbol{\lambda} - b(\mathbf{x}_i^T \boldsymbol{\lambda})) \\ &= \mathbf{y}^T \mathbf{X} \boldsymbol{\lambda} - \sum_{i=1}^n b(\mathbf{x}_i^T \boldsymbol{\lambda}) \\ &= \mathbf{s}^T \boldsymbol{\lambda} - \sum_{i=1}^n b(\mathbf{x}_i^T \boldsymbol{\lambda}), \end{aligned}$$



where  $\mathbf{X}$  is the model design matrix,  $\mathbf{s} = \mathbf{X}^T \mathbf{y}$  is the sufficient statistic, and  $b(\theta) = -\log(1 - \exp(\theta))$ .

In general, for an exponential family model (or a GLM with canonical link), the probability density of the sufficient statistic vector,  $\mathbf{S}$ , can be approximated by the formula

$$\hat{f}_{\mathbf{S}}(\mathbf{s}) = |2\pi\hat{\mathbf{I}}|^{-1/2} \exp(-\hat{l}), \quad (3.5)$$

where  $\hat{l}$  is the maximized loglikelihood, and  $\hat{\mathbf{I}}$  is the observed information matrix. This formula is originally due to Daniels [1954], although he didn't express it in likelihood notation. In our case we want to approximate a conditional probability for the column margins,  $\mathbf{s}_2$ , given the row margins,  $\mathbf{s}_1$ , where  $\mathbf{s} = (\mathbf{s}_1, \mathbf{s}_2)$ . This is accomplished by taking a ratio of two saddlepoint approximations of the form (3.5),

$$\hat{f}(\mathbf{s}_2|\mathbf{s}_1) = \frac{\hat{f}_{\mathbf{S}}(\mathbf{s})}{\hat{f}_{\mathbf{S}_1}(\mathbf{s}_1)} = \left\{ \frac{|2\pi\hat{\mathbf{I}}|}{|2\pi\hat{\mathbf{I}}_1|} \right\}^{-1/2} \exp(\hat{l}_1 - \hat{l}), \quad (3.6)$$

where  $\hat{l}_1$  is the constrained maximum of the loglikelihood, when the column effects parameters in (3.4) are all zero.

For the pathologists' ratings data, application of (3.6) results in the approximation  $\hat{f}(\mathbf{s}_2|\mathbf{s}_1) \approx 7.765 \times 10^{-10}$ . The formula (3.1) for the number of tables with the same row margins yields  $N(\mathbf{s}_1) = 2.639 \times 10^{+20}$ . Multiplying these two numbers leads to an approximate number of tables with the same margins equal to 204.9 billion.

Adding higher order terms to the saddlepoint approximation improves its accuracy, at least asymptotically. We consider two ways of correcting (3.5), both discussed in Butler [2007]. The first is an additive correction,

$$\tilde{f}_1(\mathbf{s}) = \hat{f}_{\mathbf{S}}(\mathbf{s})(1 + O),$$

and the second is its exponential counterpart suggested by McCullagh [1987, Section 6.3],

$$\tilde{f}_2(\mathbf{s}) = \hat{f}_\mathbf{s}(\mathbf{s})e^O.$$

The correction term,  $O$ , is given by the formula Butler [2007, Section 3.2.2]

$$O = \frac{1}{8}\hat{\kappa}_4 - \frac{1}{24}(2\hat{\kappa}_{23}^2 + 3\hat{\kappa}_{13}^2) \quad (3.7)$$

where  $\hat{\kappa}_4$ ,  $\hat{\kappa}_{13}$ , and  $\hat{\kappa}_{23}$  are the standardized cumulants given by

$$\hat{\kappa}_4 = \sum_{t_1, t_2, t_3, t_4} \hat{K}_{t_1 t_2 t_3 t_4} \hat{K}^{t_1 t_2} \hat{K}^{t_3 t_4},$$

$$\hat{\kappa}_{13}^2 = \sum_{t_1, t_2, t_3, t_4, t_5, t_6} \hat{K}_{t_1 t_2 t_3} \hat{K}_{t_4 t_5 t_6} \hat{K}^{t_1 t_2} \hat{K}^{t_3 t_4} \hat{K}^{t_5 t_6},$$

and

$$\hat{\kappa}_{23}^2 = \sum_{t_1, t_2, t_3, t_4, t_5, t_6} \hat{K}_{t_1 t_2 t_3} \hat{K}_{t_4 t_5 t_6} \hat{K}^{t_1 t_4} \hat{K}^{t_2 t_5} \hat{K}^{t_3 t_6},$$

where

$$\hat{K}^{t_1 t_2} = (\hat{\mathbf{I}}^{-1})_{t_1 t_2}, \quad \hat{K}_{t_1 t_2 t_3} = -\frac{\partial^3 l(\hat{\boldsymbol{\lambda}})}{\partial \lambda_{t_1} \partial \lambda_{t_2} \partial \lambda_{t_3}}, \quad \text{and} \quad \hat{K}_{ijkl} = -\frac{\partial^4 l(\hat{\boldsymbol{\lambda}})}{\partial \lambda_{t_1} \partial \lambda_{t_2} \partial \lambda_{t_3} \partial \lambda_{t_4}}.$$

Calculation of the standardized cumulants in (3.7) is usually a computationally demanding problem due to the crossed summation. However, for a GLM model the sums turn out to be separable and the standardized cumulants take simple expressions. Now we will obtain these expressions.

Recall that

$$\hat{K}_{t_1 t_2 t_3} = -l^{(3)}(\hat{\boldsymbol{\lambda}})_{t_1 t_2 t_3} = \sum_{i=1}^n b^{(3)}(\mathbf{x}_i^T \hat{\boldsymbol{\lambda}}) x_{it_1} x_{it_2} x_{it_3}$$

and

$$\hat{K}_{t_1 t_2 t_3 t_4} = -l^{(4)}(\hat{\boldsymbol{\lambda}})_{t_1 t_2 t_3 t_4} = \sum_{i=1}^n b^{(4)}(\mathbf{x}_i^T \hat{\boldsymbol{\lambda}}) x_{it_1} x_{it_2} x_{it_3} x_{it_4}.$$

We start with  $\hat{\kappa}_4$ . Let  $\{\mathbf{e}_1, \dots, \mathbf{e}_q\}$  be the standard basis of  $\mathbb{R}^q$  where  $q$  is the dimension of vectors  $\{\mathbf{x}_i\}_{i=1}^n$ . It is easy to see that

$$\hat{K}^{t_1 t_2} = (\hat{K}'')_{t_1 t_2}^{-1} = \mathbf{I}_{t_1 t_2}^{-1} = \mathbf{e}_{t_1}^T \mathbf{I}^{-1} \mathbf{e}_{t_2} \quad \text{and} \quad x_{it_1} = \mathbf{e}_{t_1}^T \mathbf{x}_i. \quad (3.8)$$

Using representations (3.8) the standardized cumulant  $\hat{\kappa}_4$  equal to

$$\sum_{t_1, t_2, t_3, t_4} \hat{K}_{t_1 t_2 t_3 t_4} \hat{K}^{t_1 t_2} \hat{K}^{t_3 t_4} = \sum_{t_1, t_2, t_3, t_4} \sum_{i=1}^n b^{(4)}(\mathbf{x}_i^T \hat{\boldsymbol{\lambda}}) x_{it_1} x_{it_2} x_{it_3} x_{it_4} \hat{\mathbf{I}}_{t_1 t_2}^{-1} \hat{\mathbf{I}}_{t_3 t_4}^{-1}$$

can be rewritten as

$$\sum_{i=1}^n b^{(4)}(\mathbf{x}_i^T \hat{\boldsymbol{\lambda}}) \sum_{t_1, t_2, t_3, t_4} \mathbf{x}_i^T \mathbf{e}_{t_1} \mathbf{e}_{t_1}^T \mathbf{I}^{-1} \mathbf{e}_{t_2} \mathbf{e}_{t_2}^T \mathbf{x}_i \mathbf{x}_i^T \mathbf{e}_{t_3} \mathbf{e}_{t_3}^T \mathbf{I}^{-1} \mathbf{e}_{t_4} \mathbf{e}_{t_4}^T \mathbf{x}_i.$$

Notice that now we can separate the sums over  $t_1, t_2, t_3, t_4$  and each sum of the form  $\sum_t \mathbf{e}_t \mathbf{e}_t^T$  is the identity matrix. Therefore, we obtain

$$\hat{\kappa}_4 = \sum_{i=1}^n b^{(4)}(\mathbf{x}_i^T \hat{\boldsymbol{\lambda}}) (\mathbf{x}_i^T \mathbf{I}^{-1} \mathbf{x}_i)^2.$$

Similarly, it can be shown that

$$\hat{\kappa}_{13}^2 = \sum_{i_1=1}^n \sum_{i_2=1}^n b^{(3)}(\mathbf{x}_{i_1}^T \hat{\boldsymbol{\lambda}}) b^{(3)}(\mathbf{x}_{i_2}^T \hat{\boldsymbol{\lambda}}) \left( \mathbf{x}_{i_1}^T \hat{\mathbf{I}}^{-1} \mathbf{x}_{i_1} \right) \left( \mathbf{x}_{i_2}^T \hat{\mathbf{I}}^{-1} \mathbf{x}_{i_2} \right) \left( \mathbf{x}_{i_2}^T \hat{\mathbf{I}}^{-1} \mathbf{x}_{i_1} \right)$$

and

$$\hat{\kappa}_{23}^2 = \sum_{i_1=1}^n \sum_{i_2=1}^n b^{(3)}(\mathbf{x}_{i_1}^T \hat{\boldsymbol{\lambda}}) b^{(3)}(\mathbf{x}_{i_2}^T \hat{\boldsymbol{\lambda}}) \left( \mathbf{x}_{i_1}^T \hat{\mathbf{I}}^{-1} \mathbf{x}_{i_2} \right)^3.$$

In the case of the double-saddlepoint approximation using the correction in the numerator and denominator leads to

$$\tilde{f}_1(\mathbf{s}_2 | \mathbf{s}_1) = \hat{f}(\mathbf{s}_2 | \mathbf{s}_1) (1 + O_{\mathbf{s}_1, \mathbf{s}_2} - O_{\mathbf{s}_1})$$

and

$$\tilde{f}_2(\mathbf{s}_2 | \mathbf{s}_1) = \hat{f}(\mathbf{s}_2 | \mathbf{s}_1) \exp\{O_{\mathbf{s}_1, \mathbf{s}_2} - O_{\mathbf{s}_1}\},$$

respectively. The estimated number of the tables is then

$$\tilde{N}_i(\mathbf{s}_1, \mathbf{s}_2) = N(\mathbf{s}_1) \tilde{f}_i(\mathbf{s}_2 | \mathbf{s}_1), \quad (3.9)$$

for  $i = 1, 2$ , where  $N(\mathbf{s}_1)$ , the exact number of the tables with a fixed  $\mathbf{s}_1$ , is given by (3.1).

The approximation of Gail and Mantel [1977] involves an application of the central limit theorem to column totals of a rectangular table. Not surprisingly then, the approximation improves as the number of rows increases, with the order of magnitude of the error being  $O(r^{-1/2})$ . The proportionality constant in the error term is a function of the number of columns in the table. In general the accuracy can be expected to deteriorate as  $c$  increases. In the same context the saddlepoint approximations (3.5) and (3.6) are in error by only  $O(r^{-1})$ . This is reduced further to  $O(r^{-2})$  by second-order correction [Butler, 2007, Section 3.2]. As with the simple normal approximation, these orders of magnitude must be tempered by the number of columns in the table. More generally we can expect the accuracy of the saddlepoint and corrected saddlepoint approximations to improve as the degrees of freedom associated with the full model, with sufficient statistics, increases relative to the dimension of the statistic  $\mathbf{s}_2$ .

### 3.4 Additional Constraints and Multi-way Tables

It is clear, in principle, that the double saddlepoint approximation extends to multi-way tables, since the number of tables with one margin fixed is also known in this case. In addition, it is often the case that the independence assumption for a two-way (or multi-way) contingency table is unreasonable. In such cases one can attempt to describe the dependence in a parsimonious way by placing restrictions on interaction terms.

The most general setting is as follows. Consider the set  $\Gamma$  consisting of all non-negative integer vectors,  $\mathbf{y}$ , satisfying a set of linear constraints,  $\mathbf{X}^T \mathbf{y} = \mathbf{s}$ , where  $\mathbf{X} \in \mathbb{Z}^{n \times q}$  and  $\mathbf{s} \in \mathbb{Z}^q$ ; that is,

$$\Gamma := \{ \mathbf{y} \in \mathbb{N}^n : \mathbf{X}^T \mathbf{y} = \mathbf{s}, \mathbf{y} \geq \mathbf{0} \} .$$

We assume, without loss of generality, that  $\mathbf{X}$  is full column rank. For example, if  $\mathbf{y}$  consists of the counts from an  $r \times c$  table with fixed margins, then  $n = rc$  and  $q = r + c - 1$ . Suppose  $\mathbf{X} = (\mathbf{X}_1, \mathbf{X}_2)$  is a partition of the columns of  $\mathbf{X}$ , and let  $(\mathbf{s}_1, \mathbf{s}_2) = (\mathbf{X}_1^T \mathbf{y}, \mathbf{X}_2^T \mathbf{y})$  be the corresponding partition of  $\mathbf{s}$ . Suppose that the cardinality of the set  $\Gamma_1 := \{ \mathbf{y} \in \mathbb{N}^n : \mathbf{X}_1^T \mathbf{y} = \mathbf{s}_1, \mathbf{y} \geq \mathbf{0} \}$  is known. Then the double saddlepoint approximation described in the previous section, and its corrected version (3.9), can be used to approximate the cardinality of  $\Gamma$ .

The most general loglinear association model for an  $r \times c$  contingency table has a canonical linear predictor of the form

$$\theta_{ij} = \lambda + \lambda_i^R + \lambda_j^C + \lambda_{ij}^{RC} \tag{3.10}$$

for  $i = 1, \dots, r$  and  $j = 1, \dots, c$ . A special case is the uniform association (UA) model in which  $\lambda_{ij}^{RC} = \beta ij$ . This model describes the dependence between the row and column factors in terms of a single parameter,  $\beta$ . The model implies that all local odds-ratios (from tables formed by the intersection of two adjacent rows and two adjacent columns) are equal to  $e^\beta$  – hence the name “uniform association”. The sufficient statistics for the UA model include the row and column margins and, in addition, the sum of products of row and column numbers weighted by the cell counts. Other examples include quasi-independence (QI),  $\lambda_{ij}^{RC} = 0$  if  $i \neq j$ , and diagonal (D),  $\lambda_{ij}^{RC} = 0$  if  $i \neq j$  and  $\lambda_{ii}^{RC} = \lambda$ , association models, as well as the independence model (I) considered earlier.

The generalization of (3.10) to a three-way,  $I \times J \times K$ , contingency table is

$$\theta_{ijk} = \lambda + \lambda_i^R + \lambda_j^C + \lambda_k^Z + \lambda_{ij}^{RC} + \lambda_{ik}^{RZ} + \lambda_{jk}^{CZ} + \lambda_{ijk}^{RCZ}$$

for  $i = 1, \dots, I$ ,  $j = 1, \dots, J$ , and  $k = 1, \dots, K$ , where  $Z$  denotes the nominal-scale factor associated with the third dimension. As in the two-way case, associations between the three factors are modeled by placing restrictions on the interaction terms. Some widely-used examples are given in Table 3.1. The models are nested in the sense that each successive model imposes a subset of the restrictions in the previous one. Since, the dimension of the statistic,  $s$ , increases with the model complexity, the number of possible tables with the same value of  $s$  decreases.

Table 3.1: Some common loglinear association models for three-way tables [see Agresti, 1990, p.144]. Model 1 implies the factors, R, C, and Z, are mutually independent; Model 2 implies Z is jointly independent of R and C; Model 3 implies R and Z are conditionally independent given C; and Model 4 implies a homogeneous pattern of conditional association between R and C across all levels of Z.

Model	Interaction constraints
M1. (R,C,Z)	$\lambda_{ijk}^{RCZ} = 0$ $\lambda_{ik}^{RZ} = 0$ $\lambda_{jk}^{CZ} = 0$ $\lambda_{ij}^{RC} = 0$
M2. (RC,Z)	$\lambda_{ijk}^{RCZ} = 0$ $\lambda_{ik}^{RZ} = 0$ $\lambda_{jk}^{CZ} = 0$
M3. (RC,CZ)	$\lambda_{ijk}^{RCZ} = 0$ $\lambda_{ik}^{RZ} = 0$
M4. (RC,RZ,CZ)	$\lambda_{ijk}^{RCZ} = 0$

Now consider the general case of an  $M$ -way contingency table. Loglinear models for  $M$ -way contingency tables can usually be expressed in the form,

$$\theta_{i_1 i_2 \dots i_M} = \lambda_{i_1 i_2 \dots i_M}^{\mathcal{T}_1} + \lambda_{i_1 i_2 \dots i_M}^{\mathcal{T}_2} + \dots + \lambda_{i_1 i_2 \dots i_M}^{\mathcal{T}_d},$$

where  $i_k = 1, \dots, I_k$ ,  $k = 1, \dots, d$  and  $\{\mathcal{T}_1, \mathcal{T}_2, \dots, \mathcal{T}_d\}$  are lower dimensional tables obtained by collapsing over one or more margins. For example, the model (RC,CZ) for a

three-way table can be represented as follows. Let  $\mathcal{T}_1$  be the table obtained by collapsing over the levels of Z, and let

$$\lambda_{i_1 i_2 i_3}^{RC} = \lambda + \lambda_{i_1}^R + \lambda_{i_2}^C + \lambda_{i_1 i_2}^{RC}. \quad (3.11)$$

Similarly,  $\mathcal{T}_2$  is obtained by collapsing over levels of R, and

$$\lambda_{i_1 i_2 i_3}^{CZ} = \lambda + \lambda_{i_2}^C + \lambda_{i_3}^Z + \lambda_{i_2 i_3}^{CZ}. \quad (3.12)$$

The model (RC,CZ) is obtained by combining (3.11) and (3.12) and ignoring redundant parameters,

$$\theta_{i_1 i_2 i_3} = \lambda_{i_1 i_2 i_3}^{RC} + \lambda_{i_1 i_2 i_3}^{CZ} = \lambda + \lambda_{i_1}^R + \lambda_{i_2}^C + \lambda_{i_3}^Z + \lambda_{i_1 i_2}^{RC} + \lambda_{i_2 i_3}^{CZ},$$

where  $i_k = 1, \dots, I_k, k = 1, 2, 3$ .

### 3.5 Examples

To approximate the number of  $r \times c$  tables with fixed marginal totals and additional constraints we can apply the formula (3.6) with  $\mathbf{s}$  equal to the full vector of sufficient statistics and  $\mathbf{s}_1$  equal to the sub-vector of row (or column) marginal totals. This results in an approximation to the conditional probability that the column marginal totals and the additional sufficient statistic take their observed values conditional on the row margins. This, in turn, can be multiplied by the known number of tables with the same row margins to get an approximation to the number of tables meeting all sufficiency constraints. The same approach can be applied in multi-way tables with  $\mathbf{s}_1$  equal to any one of the table margins.

All results in this section were obtained by using a user-friendly R routine available from the corresponding author's web site. Most of the calculations are essentially in-

stantaneous. The most demanding example involving a six-way table took 2.23 seconds on a desktop with a 2.4Ghz processor and 1.5Gb of RAM.

Tables 3.3, 3.4, 3.5 and 3.6 summarize the accuracy of the double saddlepoint approximation, and the additive and exponential corrections, for approximating the numbers of contingency tables with different linear constraints on the counts. Table 3.3 concerns  $5 \times 5$  tables constrained to have the same sufficient statistics as the pathologists' ratings data assuming I, UA, QI and D loglinear association models. Table 3.4 gives the analogous results for  $4 \times 4$  tables using the sexual fun data reported in Hout et al. [1987] [see also Agresti, 1990, p.32]. Table 3.5 gives results for  $2 \times 2 \times 8$  tables with marginal totals equal to those from a smoking and lung cancer study in eight Chinese cities [Agresti, 1996, p.60]. Table 3.6 concerns a multi-way table setting with marginal totals determined by six binary variables for coronary heart disease coded as  $\{A, B, C, D, E, F\}$  [see Edwards and Havránek, 1985].

The value tabulated for each approximation is its accuracy, defined as (signed) percentage relative error

$$\text{PRE}(\hat{N}) = 100 \times \frac{\hat{N} - N}{N}$$

where  $N$  is the exact number of the tables satisfying the relevant set of constraints. For multi-way tables we additionally report the degrees of freedom for each model considered and the actual value of the correction term  $O$ . In every case the exponentially corrected approximation is the most accurate, and in many cases the improvement over the uncorrected double saddlepoint is substantial. Also, the exponentially corrected approximation is not affected much by which margin is conditioned upon. In general the accuracy of the approximation decreases as the dimension of the statistic,  $s$ , increases relative to the number of cells in the table. This is to be expected because, the larger the dimension of  $s$ , the smaller the degrees of freedom, and the fewer counts being summed



over. In Table 3.5 the least accurate approximation was for the homogeneous association model, (RC,RZ,CZ), which, for a  $2 \times 2 \times 8$  table, has 25 parameters leaving only 7 degrees of freedom.

Table 3.2: Six models for the coronary heart disease data from [Edwards and Havránek, 1985].

Model	DF
M1. [A, B, C, D, E, F]	57
M2. [ABCD, DEF]	42
M3. [ABCDE]	32
M4. [ABCDE, ACDEF]	16
M5. [ABCDE, ACDEF, BCDF]	12
M6. [ABCDE, ACDEF, BCDF, ABDEF, ABCF, BCEF]	4

The results for the coronary heart disease data are reported in Table 3.6. We applied the approximation to determine the number of six way tables meeting sufficiency constraints determined by several different models that might be plausible for this data. These models are listed in Table 3.2. Notice that models 3 through 6 are nested in the same sense as the models in Table 3.1. Also, model 1 is nested in model 2, but model 2 is not nested in model 3. In addition, we note that the degrees of freedom of the models is monotonically decreasing.

The choice of the margin did not affect the first four significant digits of the approximations, and results are reported only for margin A. Since we do not know the exact number of the tables for models 1-3, we cannot report the PRE, and the value of  $\tilde{N}_2$  is given in place of  $N$  in these cases. For the models 4-6 the degrees of freedom are small enough that exact algebraical computation (see Section 3.7.1) are feasible. In

these cases additive correction is worse than the uncorrected version. The exponential correction provides an acceptable level of accuracy for these cases considering the small number of degrees of freedom. The pattern of the dependence between the PRE on the one hand and degrees of freedom and the correction term  $O$  on the other observed in Table 3.5 cannot be directly extrapolated to the missing part of Table 3.6 largely due to the worse performance of the additive correction. Nevertheless, these values suggest we can expect good relative accuracy of the exponential correction for models 1, 2, and 3. An insightful discussion about why the additive correction may not be asymptotically correct in particular situations in which the exponential correction must be used can be found in Shun and McCullagh [1995] [see also Butler, 2007, Section 3.4].

Table 3.3: Percentage relative errors of the double saddlepoint approximation, and higher-order corrections, for the numbers of  $5 \times 5$  tables meeting the same set of linear constraints as the pathologists' ratings data from Agresti [1990, p.368]

Model	Margin	$\hat{N}$	$\tilde{N}_1$	$\tilde{N}_2$	$N$
I	Row	+4.18	-3.36	-3.10	$1.933 \times 10^{11}$
	Column	+5.92	-3.51	-3.11	
UA	Row	+16.17	-8.78	-6.28	34,670
	Column	+14.26	-9.02	-6.80	
QI	Row	+31.12	-9.19	-3.58	435
	Column	+45.11	-14.29	-3.63	
D	Row	+23.08	-7.59	-4.07	1,132,576
	Column	+21.07	-7.09	-4.06	

Table 3.4: Percentage relative errors of the double saddlepoint approximation, and higher-order corrections, for the numbers of  $4 \times 4$  tables meeting the same set of linear constraints as the sexual fun data from Agresti [1990, p.32]

Model	Margin	$\hat{N}$	$\tilde{N}_1$	$\tilde{N}_2$	$N$
I	Row	-12.61	-1.95	-1.27	947,766,430
	Column	-12.67	-1.95	-1.27	
UA	Row	-12.08	-2.32	-1.76	8,137,492
	Column	-12.15	-2.33	-1.76	
QI	Row	+27.64	-12.00	-6.43	15,708
	Column	+27.55	-11.97	-6.43	
D	Row	-13.79	-3.83	-3.24	27,209,031
	Column	-13.85	-3.84	-3.24	

### 3.6 Counting Tables of Zeros and Ones

The number of tables with only 0-1 entries meeting linear constraints can also be approximated based on a GLM formulation. This case requires a logistic model for binary observations instead of the geometric model discussed above. Specifically, suppose that  $\{Y_{ij}\}$  is an  $r \times c$  table of independent binary counts with associated success probabilities  $\{\pi_{ij}\}$ . Consider a model of the form (3.4), where  $\theta$  is now the logit of  $\pi$ . Once again the marginal totals are the sufficient statistics, and hence the conditional distribution given the margins is independent of the parameters. In particular, if  $\lambda_1^C = \dots = \lambda_c^C = 0$ , the conditional distribution of the counts in each row, given the row margins, is uniform over the set of all possible assignments of the zeros and ones; that is, every possible assignment in row  $i$  has probability  $\binom{c}{y_i}^{-1}$

Table 3.5: Percentage relative errors of the double saddlepoint approximation, and higher order corrections, for the numbers of  $2 \times 2 \times 8$  tables with the same sufficient statistics as the Chinese smoking and lung cancer data from Agresti [1996, p.60] under various loglinear association models.

Model	Margin	DF	$\hat{N}$	$\tilde{N}_1$	$\tilde{N}_2$	$N$
M1	$I$	22	+3.93	-0.12	-0.04	$3.918 \times 10^{54}$
(R,C,Z)	$J$	22	+3.93	-0.12	-0.04	
	$K$	22	-11.06	-0.64	-0.01	
M2	$I$	21	+4.85	-1.22	-1.05	$2.530 \times 10^{51}$
(RC,Z)	$J$	21	+4.85	-1.22	-1.05	
	$K$	21	-10.28	-1.46	-1.02	
M3	$I$	14	+63.83	-24.37	-4.37	$3.425 \times 10^{33}$
(RC,CZ)	$J$	14	+63.83	-24.37	-4.37	
	$K$	14	+40.18	-13.38	-4.34	
M4	$I$	7	+135.35	-85.14	-7.77	$2.262 \times 10^{15}$
(RC,RZ,CZ)	$J$	7	+135.35	-85.14	-7.77	
	$K$	7	+101.37	-55.82	-7.74	

For an illustration, consider Darwin's data concerning the presence or absence of 13 species of finch in 17 Galápagos islands [see Liu, 2001, p.93]. The exact number of tables with the same margins as this dataset is given in Chen et al. [2005, Section 6.1]. To four significant figures it is  $6.715 \times 10^{16}$ . Percentage relative errors of the double saddlepoint approximation, and the additive and exponential corrections are given in Table 3.7. In this case the uncorrected double saddlepoint is off by over 200%, and the additive correction over-corrects, resulting in a negative estimate. However, the exponentially corrected double saddlepoint is almost exact, with a relative error significantly

Table 3.6: Percentage relative errors of the double saddlepoint approximation, and higher order corrections, for the numbers of six-way tables with the same sufficient statistics as the Czech coronary heart disease data from Edwards and Havránek [1985]. ( $N^* = N$  for models M4-M6.  $N^* = \tilde{N}_2$  for models M1-M3.)

Model	DF	$O$	$\hat{N}$	$\tilde{N}_1$	$\tilde{N}_2$	$N^*$
M1	57	0.11	-	-	-	$5.627 \times 10^{93}$
M2	42	-0.21	-	-	-	$2.414 \times 10^{60}$
M3	32	-1.33	-	-	-	$3.411 \times 10^{52}$
M4	16	-1.97	424.61	-610.76	-27.10	$9.191 \times 10^{18}$
M5	12	-3.15	1749.91	-4094.25	-21.44	$1.672 \times 10^{11}$
M6	4	-21.44	2877.05	-9122.68	-47.12	810

less than 1%.

The formulas (3.2) and (3.3) can be modified so that they apply in the case of 0-1 tables by putting a negative sign in front of  $\alpha$  and  $\alpha_1$ , respectively. The modification of (3.2) yields the value  $2.725 \times 10^{26}$  for Darwin's finch data which is a very poor approximation. In contrast, Bender's approximation (3.3) performs quite well giving  $9.976 \times 10^{16}$ . However, the double saddlepoint approximation with the exponential correction is considerably better than either of these alternatives.

In principle the logistic model discussed in this section can be extended to deal with multiway tables of zeros and ones in the same way that the geometric model was extended in Section 3.4. However, we have not investigated the performance of this generalization in practice.

Table 3.7: Percentage relative errors of the double saddlepoint approximation, and higher-order corrections, for the number of  $13 \times 17$  tables of zeros and ones with the same margins as Darwin’s finch data.

Margin	$\hat{N}$	$\tilde{N}_1$	$\tilde{N}_2$	$N$
Row	302.9	-258.1	0.131	$6.715 \times 10^{16}$
Column	238.3	-174.0	0.030	

### 3.7 Other Counting Methods

#### 3.7.1 Exact Algebraic Computation

The problem of counting the number of contingency tables meeting certain linear constraints is equivalent to counting the set of integral points of a rational convex polytope of the form

$$\mathbf{P} := \{ \mathbf{y} \in \mathbb{R}^d : \mathbf{X}^T \mathbf{y} = \mathbf{s}, \mathbf{y} \geq \mathbf{0} \} ,$$

where  $\mathbf{X} \in \mathbb{Z}^{d \times f}$  and  $\mathbf{s} \in \mathbb{Z}^f$ . If we now define the generating function,

$$f(\mathbf{P}; \mathbf{y}) = \sum_{\alpha \in \mathbf{P} \cap \mathbb{Z}^d} \mathbf{y}^\alpha ,$$

then  $|\mathbf{P} \cap \mathbb{Z}^d| = f(\mathbf{P}; \mathbf{1})$ .

As an example, suppose that  $\mathbf{P}$  is the one-dimensional polytope  $[0, t]$ . Then,  $f(\mathbf{P}; x) = 1 + x + x^2 + \dots + x^t$ ,  $f(\mathbf{P}; x)$  can be represented by the rational function  $\frac{1-x^{t+1}}{1-x}$ , and  $f(\mathbf{P}; 1) = t + 1$ , the number of integer points in  $\mathbf{P}$ . Note that substituting  $x = 1$  yields a denominator equal to zero in the rational function, so some analytic technique must be used to evaluate  $f(\mathbf{P}; 1)$ . In this particular case, we could take the limit as  $x$  approaches 1 and apply l’Hospita’s rule. In general, we must use more complicated

residue calculus as described in Barvinok [1994]. The exact answers for the examples in Tables 3.3 and 3.4 each took less than 30 seconds using a C++ implementation of Barvinok's algorithm available at <http://www.math.ucdavis.edu/~latte> [DeLoera et al., 2004]. For the examples in Table 3.5 the computations took 4450, 1209, and 85 seconds for Models 1-3 respectively, and less than 1 second for Model 4. For the results in Table 3.6 the computations took 255 and 4.2 seconds for Models 4 and 5, respectively and less than 1 second for Model 6. For Models 1, 2, and 3 the enumeration was terminated after four days. Other analytical methods have been developed which are faster in special cases such as counting two-way tables with fixed margins [Beck, 2000]. For a recent review, see Yoshida [2004]. The computing time for algebraic methods can be prohibitive for larger tables. However, this is precisely the situation in which the saddlepoint approximation is likely to be most accurate because the dimension of  $s$  relative to the number of cells in the table generally decreases as the dimensions of the table grow.

### 3.7.2 Importance Sampling

Let  $q : \Gamma \rightarrow \mathbb{R}$  be a probability mass function which assigns positive probability to all vectors,  $\mathbf{y}$ , in the finite set  $\Gamma$ . Then the cardinality of  $\Gamma$  can be expressed as

$$|\Gamma| = \sum_{\mathbf{y} \in \Gamma} 1 = \sum_{\mathbf{y} \in \Gamma} \frac{1}{q(\mathbf{y})} q(\mathbf{y}) = E_q \left\{ \frac{1}{q(\mathbf{y})} \right\}.$$

Hence, if it is possible to simulate an i.i.d. sequence,  $\mathbf{y}_1, \dots, \mathbf{y}_N$ , from  $q$ , and to evaluate,  $q(\mathbf{y}_i)$ ,  $i = 1, \dots, N$ , then a Monte Carlo approximation to  $|\Gamma|$  is given by

$$\widehat{|\Gamma|} = \frac{1}{N} \sum_{i=1}^N \frac{1}{q(\mathbf{y}_i)}.$$

For example, Chen et al. [2005] construct a probability mass function for counting two-way tables with fixed margins of the form

$$q(\mathbf{y}) = q_1(y_1)q_2(y_2|y_1) \cdots q_d(y_d|y_{-d}),$$

where  $y_{-d}$  denotes the vector  $y$  excluding its  $d$ th element. Since the approximation is the mean of an i.i.d. sample, standard errors for  $|\widehat{\Gamma}|$ , and hence confidence intervals for  $|\Gamma|$ , can also be constructed. Chen et al. [2005] also develop an importance sampling method for counting two-way zero-one tables with fixed margins. Chen et al. [2006] extended this method to multi-way tables with complicated linear constraints. In particular, they report an estimate for the total number of the tables in model M6 of Table 3.2 to be 841, which is very close to the exact number 810. It is clear that Monte Carlo methods are a useful and powerful alternative to analytical approximation in the counting problems considered in this paper.

### 3.8 Discussion

We have proposed a new way of approximating the number of contingency tables, and tables of zeros and ones, that satisfy certain linear constraints. The approximations involve fitting generalized linear models which can be accomplished almost instantaneously. The approximations are much more accurate than analytical approximations that have been proposed previously, and can be applied in a wider range of problems. In addition, they can be applied in problems for which exact algebraic methods are not yet computationally feasible.



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## CHAPTER 4

### APPENDIX

#### 4.1 Notations

We denote by capital letter  $\mathbf{D}$  a matrix and by regular size letter  $\mathbf{y}$  a vector. Let  $N = n_1 + \dots + n_n$ . We assume that the following quantities are observed

$$\mathbf{y} = \begin{pmatrix} \mathbf{y}_1 \\ \vdots \\ \mathbf{y}_n \end{pmatrix}_{N \times 1} \quad \mathbf{Z} = \begin{pmatrix} \mathbf{z}_1 & \dots & \mathbf{z}_n \end{pmatrix}_{q \times N} \quad \mathbf{X} = \begin{pmatrix} \mathbf{X}_1 & \dots & \mathbf{X}_n \end{pmatrix}_{p \times N} \quad (4.1)$$

We will consider the following vectors.

$$\mu_{N \times 1}; \mathbf{b}'(\mu)_{N \times 1}; \mathbf{b}''(\mu)_{N \times 1}; \mathbf{g}'(\mu)_{N \times 1}. \quad (4.2)$$

$\mathbf{W} = \text{diag}(\mathbf{W}_1, \dots, \mathbf{W}_{n_n})$  is a  $N \times N$  diagonal matrix depending on  $\mathbf{Y}, \mathbf{X}, \mathbf{Z}, \mathbf{u}, \theta$  but we will suppress the first three which are observable. So we will write  $W(\mathbf{u}; \theta)$  and

$$W_{ij} = \frac{w_{ij}}{b''(\mu_{ij})g'(\mu_{ij})^2} \quad (4.3)$$

$\sigma$  in  $\mathbf{D}(\sigma)$  shows the dependence on a value of parameter  $\sigma$ . Operation  $\odot$  will denote componentwise multiplication. For example, if  $\mathbf{A} = (a_{ij}), \mathbf{B} = (b_{ij})$  are matrices of the same size  $n \times m$  then  $\mathbf{C} = \mathbf{A} \odot \mathbf{B}$  is a  $n \times m$  matrix with  $c_{ij} = a_{ij}b_{ij}$ . Operation  $\text{vec}$  is vectorization operation. It transforms a  $n \times m$  matrix  $\mathbf{A} = (\mathbf{a}_1, \dots, \mathbf{a}_m)$  into  $nm \times 1$  vector by consequently stacking columns  $\{\mathbf{a}_i\}$ . Operation  $\text{vech}$  can be applied only to a square symmetric  $n \times n$  matrix  $A$  and it stacks only the distinct entries of  $\mathbf{A}$  on or below the main diagonal. The result of this operation is a  $n(n+1)/2$  column vector  $(a_{11}, \dots, a_{n1}, a_{22}, \dots, a_{n2}, \dots, a_{nn})'$ .

## 4.2 Construction of the matrix $\mathbf{G}$

Here, we show how matrix  $\mathbf{G}$  from the equation  $\mathbf{G}\sigma = \text{vech}(\mathbf{D})$  may be found. Computationally, one would only need to keep non-zero elements. Let us assume there are exactly  $q_1$  non-zero elements of matrix  $\mathbf{D}$  and  $q_*$  unique elements which are the entries of the vector  $\sigma$ . We represent  $\mathbf{G} = \mathbf{G}^{(1)}\mathbf{G}^{(2)}$  where  $\mathbf{G}^{(1)}$  of size  $q(q+1)/2 \times q_1$  and  $\mathbf{G}^{(2)}$  of size  $q_1 \times q_*$ . If  $D_{ij}, i \leq j$  is the  $k$ th non-zero element of  $\text{vech}(\mathbf{D})$  then  $G_{(j-1)(q-j/2)+i,k}^{(1)} = 1$ . Set the other elements of  $\mathbf{G}^{(1)}$  to zero. Let  $\mathbf{d} = (\mathbf{G}^{(1)T}\mathbf{G}^{(1)})^{-1}\mathbf{G}^{(1)T}\text{vech}(\mathbf{D})$ . Then,  $G_{ij}^{(2)} = I_{\{d_i=\sigma_j\}}$  for  $i = 1, \dots, q_1$  and  $j = 1, \dots, q_*$ .

## 4.3 Implementation of Step 1 of the SR approximation

In this section we provide details of how to numerically perform Step 1 of the SR rule.

Let us recall that at Step 1 we want to find the mode  $\hat{\mathbf{u}}_i$  of

$$f(\mathbf{u}_i|\mathbf{y}_i; \boldsymbol{\psi}^{(s)}) = \frac{f(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)})}{f(\mathbf{y}_i; \boldsymbol{\psi}^{(s)})} = \frac{\exp \left\{ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)}) - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i \right\}}{\int_{\mathbb{R}^q} \exp \left\{ a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)}) - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i \right\} d\mathbf{u}_i} \quad (4.4)$$

It is obvious that  $f(\mathbf{u}_i|\mathbf{y}_i; \boldsymbol{\psi}^{(s)})$  has the same mode as the function  $h(\mathbf{u}_i) = a(\mathbf{y}_i, \mathbf{u}_i; \boldsymbol{\psi}^{(s)}) - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i$ . Notice that  $h(\mathbf{u}_i) = \sum_{j=1}^{n_i} \left( w_{ij} [y_{ij} \theta_{ij}^{(s)} - b(\theta_{ij}^{(s)})] \right) - \frac{1}{2} \mathbf{u}_i^T \mathbf{u}_i$  is globally concave, therefore, Newton-Raphson algorithm with step-halving should work well. Then the updating scheme is given by

$$\mathbf{u}^{(m+1)} = \mathbf{u}^{(m)} - \frac{1}{2^k} \left[ \frac{\partial^2 h(\mathbf{u}^{(m)})}{\partial \mathbf{u} \partial \mathbf{u}^T} \right]^{-1} \frac{\partial h(\mathbf{u}^{(m)})}{\partial \mathbf{u}} \quad (4.5)$$

where  $k$  is the smallest non-negative integer which guarantees that  $h(\mathbf{u}^{(m+1)}) > h(\mathbf{u}^{(m)})$ . Let us find the gradient and the Hessian of  $h(\mathbf{u})$ . The gradient is

$$\frac{\partial h(\mathbf{u}_i)}{\partial \mathbf{u}} = \mathbf{D}^T \sum_{j=1}^{n_i} \frac{w_{ij} [y_{ij} - \mu_{ij}]}{b'(\theta_{ij}) g'(\mu_{ij})} \mathbf{z}_{ij} - \mathbf{u}_i = \mathbf{D}^T \mathbf{Z}_i \mathbf{W}_i [\mathbf{g}'(\boldsymbol{\mu}_i) \odot (\mathbf{y}_i - \boldsymbol{\mu}_i)] - \mathbf{u}_i \quad (4.6)$$

which can be written as

$$\frac{\partial h(\mathbf{u}_i)}{\partial \mathbf{u}} = \mathbf{D}^T \mathbf{Z}_i \mathbf{W}_i [(\mathbf{b}''(\theta_i^{(s)}))^{-1} \odot (\mathbf{y}_i - b'(\theta_i^{(s)}))] - \mathbf{u}_i \quad (4.7)$$

In case of the canonical link we get

$$\frac{\partial h(\mathbf{u}_i)}{\partial \mathbf{u}} = \mathbf{D}^T \mathbf{Z}_i [\mathbf{w}_i \odot (\mathbf{y}_i - b'(\theta_i^{(s)}))] - \mathbf{u}_i \quad (4.8)$$

In the previous equation  $\mathbf{w}_i = (w_{i1}, \dots, w_{in_i})$ . For the Hessian we have

$$\frac{\partial^2 h(\mathbf{u})}{\partial \mathbf{u} \partial \mathbf{u}^T} = \sum_{j=1}^{n_i} w_{ij} \left[ -\mathbf{D}^T \frac{\mathbf{z}_{ij} \mathbf{z}_{ij}^T}{b''(\theta_{ij}) g'(\mu_{ij})^2} \mathbf{D} \right] - \mathbf{I}_q \quad (4.9)$$

or

$$\frac{\partial^2 h(\mathbf{u})}{\partial \mathbf{u} \partial \mathbf{u}^T} = -\mathbf{D}^T \left( \sum_{j=1}^{n_i} \frac{w_{ij} \mathbf{z}_{ij} \mathbf{z}_{ij}^T}{b''(\theta_{ij}) g'(\mu_{ij})^2} \right) \mathbf{D} - \mathbf{I}_q = -(\mathbf{I}_q + \mathbf{D}^T \mathbf{Z}_i \mathbf{W}_i \mathbf{Z}_i^T \mathbf{D}) \quad (4.10)$$

Then a procedure similar to IRLS can be developed. The  $m$ th iteration is defined as

$$(\mathbf{I}_q + \mathbf{D}^T \mathbf{Z}_i \mathbf{W}_i^{(m)} \mathbf{Z}_i^T \mathbf{D}) \mathbf{u}_i^{(m+1)} = \mathbf{D}^T \mathbf{Z}_i \mathbf{W}_i^{(m)} \mathbf{t}_i^{(m)} + \left(1 - \frac{1}{2^k}\right) \mathbf{u}_i^{(m)} \quad (4.11)$$

where the working variate is

$$\mathbf{t}_i^{(m)} = \mathbf{Z}_i^T \mathbf{D} \mathbf{u}_i^{(m)} + \frac{1}{2^k} \mathbf{g}'(\mu_i^{(m)}) \odot (\mathbf{y}_i - \mu_i^{(s)}) \quad (4.12)$$

The update is therefore

$$\begin{aligned} (\mathbf{I}_q + \mathbf{D}^T \mathbf{Z}_i \mathbf{W}_i^{(m)} \mathbf{Z}_i^T \mathbf{D}) \mathbf{u}_i^{(m+1)} &= \mathbf{D}^T \mathbf{Z}_i \mathbf{W}_i^{(m)} \mathbf{Z}_i^T \mathbf{D} \mathbf{u}_i^{(m)} + \\ &\frac{1}{2^k} \mathbf{D}^T \mathbf{Z}_i (\mathbf{w}_i \odot (\mathbf{y}_i - b'(\theta_i^{(m)}))) + \left(1 - \frac{1}{2^k}\right) \mathbf{u}_i^{(m)} \end{aligned}$$

If  $n_i < q$  (rare in practice) then the following fact is useful

$$(\mathbf{I}_q + \mathbf{D}^T \mathbf{Z}_i \mathbf{W}_i^{(m)} \mathbf{Z}_i^T \mathbf{D})^{-1} = \mathbf{I}_q - \mathbf{D}^T \mathbf{Z}_i (\mathbf{Z}_i^T \Sigma \mathbf{Z}_i + (\mathbf{W}_i^{(m)})^{-1})^{-1} \mathbf{Z}_i^T \mathbf{D} \quad (4.13)$$

Notice that in the above the matrix to be inverted of size  $n_i$ .

Finally, by  $\mathbf{A}^{-1} \mathbf{b}$  we mean the solution to  $\mathbf{A} \mathbf{x} = \mathbf{b}$  which is known to be more computationally stable.

## 4.4 Computing $\xi_{ij}$

We know that  $\xi_{ij} = \mathbf{G}^T \text{vech}(\mathbf{z}_{ij} \mathbf{u}_i^T)$ . Hence, once we have got a MC sample of  $(\mathbf{u}_i^1, \dots, \mathbf{u}_i^M)$  we will need to calculate  $\xi_{ij}$   $M$  times to get  $(\xi_{ij}^1, \dots, \xi_{ij}^M)$ . However, use of  $\mathbf{G}^T \text{vech}(\mathbf{z}_{ij} \mathbf{u}_i^T)$  form is not computationally efficient for two reasons. First of all, matrix  $\mathbf{G}$  is a 0-1 matrix with only one non-zero element in each row. Hence, it is enough to store the indexes of the non-zero elements to perform the multiplication. Second, vectors  $\mathbf{z}_{ij}$ 's sometimes have a sparse structure as well. For instance, in the salamander data example  $\mathbf{z}_{ij}$ 's are twenty-dimensional but there are only two non-zero elements corresponding to a matching pair of male and female salamanders. Another example of sparse  $\mathbf{z}_{ij}$ , one can think of, is a model containing a categorical variables interacting with random effect. The algorithm described below will made use of both features providing an efficient way of calculating  $\xi_{ij}$ . In this implementation we will create a structure representations of matrix  $\mathbf{D}$ , DS (D structure).

First, let  $\mathbf{z}_{ij} = (z_{ij1}, \dots, z_{ijq})^T$  and  $\mathbf{u}_i = (u_{i1}, \dots, u_{iq})^T$  then matrix

$$\mathbf{z}_{ij} \mathbf{u}_i^T = \begin{pmatrix} z_{ij1}u_{i1} & z_{ij1}u_{i2} & \dots & z_{ij1}u_{iq} \\ z_{ij2}u_{i1} & z_{ij2}u_{i2} & \dots & z_{ij2}u_{iq} \\ \vdots & \vdots & \ddots & \vdots \\ z_{ijq}u_{i1} & z_{ijq}u_{i2} & \dots & z_{ijq}u_{iq} \end{pmatrix}_{q \times q} \quad (4.14)$$

and vector

$$\text{vech}(\mathbf{z}_{ij} \mathbf{u}_i^T) = \underbrace{(z_{ij1}u_{i1}, z_{ij2}u_{i1}, \dots, z_{ijq}u_{i1})}_q, \underbrace{(z_{ij2}u_{i2}, \dots, z_{ijq}u_{i2})}_{q-1}, \underbrace{(z_{ijq}u_{iq})}_1 \Big)_{1 \times q(q+1)/2}^T \quad (4.15)$$

Matrix  $\mathbf{D}$  coming from the Cholesky decomposition of  $\Sigma$  is a lower triangular with

positive elements on the main diagonal

$$\mathbf{DM} = \mathbf{D} = \begin{pmatrix} d_{11} & 0 & \dots & 0 \\ d_{21} & d_{22} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ d_{q1} & d_{q2} & \dots & d_{qq} \end{pmatrix} \quad (4.16)$$

with

$$\text{vech}(\mathbf{D}) = \underbrace{(d_{11}, d_{21}, \dots, d_{q1})}_q, \underbrace{(d_{22}, \dots, d_{q2})}_{q-1}, \dots, \underbrace{(d_{qq})}_1 \Big)_{1 \times q(q+1)/2}^T \quad (4.17)$$

In general, matrix  $\mathbf{D}$  can have a larger number of non-zero elements than matrix  $\mathbf{\Sigma}$ . Let us denote by  $q_1$ , ( $q \leq q_1 \leq q(q+1)/2$ ) the number of non-zero elements in  $\mathbf{D}$  and by  $q^*$ , ( $1 \leq q_1 \leq q(q+1)/2$ ) the number of unique elements of  $\mathbf{D}$ . The vector of unique covariances

$$\boldsymbol{\sigma} = (\sigma_1, \dots, \sigma_{q^*})^T \quad (4.18)$$

corresponds to

$$\boldsymbol{\xi}_{ij} = (\xi_{ij1}, \dots, \xi_{ijq^*})^T \quad (4.19)$$

Let  $m_i$ ,  $i = 1, \dots, q^*$  denote the number of times element  $\sigma_i$  is presented in matrix  $\mathbf{D}$ . It is obvious that  $m_1 + \dots + m_{q^*} = q_1$ . For each  $\sigma_i$ ,  $i = 1, \dots, q^*$  we can record the indexes of elements of matrix  $\mathbf{D}$  corresponding to  $\sigma_i$  and store them in an index table below and it is intuitively appealing to think of it in a matrix manner (but with a varying number of elements per row).

$$\text{DS.PairTable} = \text{DS.PT} = \begin{pmatrix} (k_{11}, l_{11}) & (k_{12}, l_{12}) & \dots & (k_{1m_1}, l_{1m_1}) \\ (k_{21}, l_{21}) & (k_{22}, l_{22}) & \dots & (k_{2m_2}, l_{2m_2}) \\ \vdots & \vdots & \ddots & \vdots \\ (k_{q^*1}, l_{q^*1}) & (k_{q^*2}, l_{q^*2}) & \dots & (k_{q^*m_{q^*}}, l_{q^*m_{q^*}}) \end{pmatrix} \begin{matrix} : \sigma_1 \\ : \sigma_2 \\ \vdots \\ : \sigma_{q^*} \end{matrix} \quad (4.20)$$

Notice that, knowing  $\boldsymbol{\sigma}$  and DS.PairTable is equivalent to knowing  $\mathbf{D}$ .

Now, to calculate the  $s$ th component of  $\xi_{ij}$  we look at the  $s$ th row of the DS.PairTable and multiply corresponding component of  $\mathbf{z}_{ij}$  and  $\mathbf{u}_i$  in the following fashion

$$\xi_{ijs} = z_{ijk_{s1}} u_{il_{s1}} + z_{ijk_{s2}} u_{il_{s2}} + \dots + z_{ijk_{sm_s}} u_{il_{sm_s}} \quad (4.21)$$

However, how we previously mentioned,  $\mathbf{z}_{ij}$  is sometimes sparse. It should also be incorporated in the algorithm to gain an additional efficiency. What could be done is we could ignore the rows of matrix  $\mathbf{D}$  corresponding to the zero elements of vector  $\mathbf{z}_{ij}$

$$\mathbf{D} = \begin{pmatrix} d_{11} & 0 & \dots & 0 \\ d_{21} & d_{22} & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ d_{q1} & d_{q2} & \dots & d_{qq} \end{pmatrix} \begin{array}{l} \longleftarrow \\ \longleftarrow \text{ignore} \\ \longleftarrow \\ \longleftarrow \end{array} \begin{pmatrix} z_{ij1} \\ 0 \\ \vdots \\ z_{ijq} \end{pmatrix} \quad (4.22)$$

In other words, those pairs  $(k, l)$  where the first index,  $k$ , coincides with a zero coordinate in  $\mathbf{z}_{ij}$  should be ignored while calculating  $\xi_{ij}$ . To implement this we need an additional  $q^* \times q + 1$  matrix

$$\text{DS.IndexTable} = \text{DS.IT} = \begin{pmatrix} IT_{11} & IT_{12} & \dots & IT_{1q+1} \\ IT_{21} & IT_{22} & \dots & IT_{2q+1} \\ \vdots & \vdots & \ddots & \vdots \\ IT_{q^*1} & IT_{q^*2} & \dots & IT_{q^*q+1} \end{pmatrix}. \quad (4.23)$$

For each covariance  $\sigma_s$  we have

$$\left( \underbrace{IT_{s1}, \dots, IT_{s2} - 1}_{\text{Row 1}} \mid \underbrace{IT_{s2} \dots IT_{s3} - 1}_{\text{Row 2}} \mid \dots \mid \underbrace{IT_{sq} \dots IT_{sq+1} - 1}_{\text{Row } q} \right). \quad (4.24)$$

We will store the index structure above with  $m_i$ 's as a vector of unsigned integers of size  $q^*$ . Hence, from now on by  $\text{DS.m} = (m_1, \dots, m_{q^*})$ . Therefore, DS has three slots: PairTable, IndexTable, and  $m$ .

---

**Algorithm 1:** Computing  $\xi_{ij}$ 

---

**Input:** vectors of doubles  $\mathbf{z}_{ij}$ ,  $\mathbf{u}_i$  and DS

**Output:** vector of doubles  $\xi_{ij}$

```
1 begin
2   for  $s_1 = 0$  to  $q^* - 1$  do
3      $\xi_{ij}[s_1] \leftarrow 0$ 
4     for  $s_2 = 0$  to  $q - 1$  do
5       if  $\mathbf{z}_{ij}[s_2] \neq 0$  and
6         DS.IT[ $s_1(q^* + 1) + s_2$ ] < DS.IT[ $s_1(q^* + 1) + s_2 + 1$ ] then
7          $s_3 \leftarrow$  DS.IT[ $s_1(q^* + 1) + s_2$ ]
8         while  $s_3 <$  DS.IT[ $s_1(q^* + 1) + s_2 + 1$ ] do
9            $k \leftarrow$  DS.PT[ $s_3 + +$ ]
10           $l \leftarrow$  DS.PT[ $s_3 + +$ ]
11           $\xi_{ij}[s_1] += \mathbf{z}_{ij}[k] * \mathbf{u}_i[l]$ 
12        end
13      end
14    end
15 end
```

---

Complexity of the old (matrix multiplication) implementation:

(\*):  $q^*q(q + 1)/2$ ;

(+):  $q^*q(q + 1)/2 - q^*$ .

Complexity of the new (indexing) implementation:

(\*):  $(m_1 + \dots + m_{q^*}) \leq q_1 \leq q(q+1)/2$ ;

(+):  $(m_1 + \dots + m_{q^*} - q^*)$ .

We also ignore the issues of accessing elements even though it may influence.

## 4.5 SAS-GLIMMIX code

The data files minnesota-data.txt and salamander-glimmix.txt are available from the author.

Minnesota data. The model with interaction.

```
=====
filename minnesot "minnesota-data.txt";
data minnesota;
infile minnesot;
input obs subject time event count;
proc glimmix;
class subject time event;
model count = time event time*event
/ dist=poisson solution;
random subject subject*time subject*event
type=vc;
run;
proc genmod;
class subject time event;
model count = time event time*event subject
subject*time subject*event / dist=poisson;
```



=====

**Minnesota data. The model without interaction.**

=====

```
filename minnesot "minnesota-data.txt";
data minnesota;
infile minnesot;
input obs subject time event count;
proc glimmix;
class subject time event;
model count = time event
/ dist=poisson solution;
random subject subject*time
subject*event / type=vc;
run;
```

=====

**Salamander data.**

=====

```
filename salglim "salamander-glimmix.txt";
data salamander;
infile salglim;
input obs subject crossingtype female male count;
proc glimmix METHOD=RSPL;
class subject crossingtype female male;
```

```
model count(event='1') = crossing-type
/ dist=binomial noint solution;
random subject*female subject*male / type=vc;
run;
=====
```