Approximation Methods for Mixed Models with Probit Link Functions

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Abstract

We study approximation methods for a large class of mixed models with a probit link function that includes mixed versions of the binomial model, the multinomial model, and generalized survival models. The class of models is special because the marginal likelihood can be expressed as Gaussian weighted integrals or as multivariate Gaussian cumulative density functions. The latter approach is unique to the probit link function models and has been proposed for parameter estimation in complex, mixed effects models. However, it has not been investigated in which scenarios either form is preferable. Our simulations and data example show that neither form is preferable in general and give guidance on when to approximate the cumulative density functions and when to approximate the Gaussian weighted integrals and, in the case of the latter, which general purpose method to use among a large list of methods.

Keywords: Gauss–Hermite quadrature; mixed models; multivariate normal CDF approximation; probit link; randomized quasi-Monte Carlo; stochastic spherical-radial rules
1 Introduction

Estimating mixed models with moderate-to-high dimensional random effect terms per cluster can be computationally expensive. This is particularly true for some discrete choice models in economics, family-based analysis of genetic and environmental contributions with both survival times and categorical outcomes in biostatistics, and grouped measurements with censoring. Most often, analytical expressions of the log marginal likelihood term for each cluster and the derivatives with respect to the model parameters do not exist. In this paper, we focus on a class of mixed models which have in common that the intractable log marginal likelihood terms can be written in different ways, in terms of the log of two different types of intractable integrals. The first type of intractable integrals is Gaussian weighted integrals (GWIs) for which many general integral approximation methods have been suggested. For the second type of intractable integrals, one can show that the intractable integrals can be written as multivariate normal cumulative density functions (CDFs). This is unique for this class of mixed models.

The class of models includes: mixed binomial models with a probit link such as those used by Ochi and Prentice (1984), Pawitan et al. (2004), and Lichtenstein et al. (2009); the discrete time survival submodel used by Barrett et al. (2015) as part of a joint model; mixed multinomial models with a probit link such as in the conditional model used by Girolami and Rogers (2006); mixed ordinal models, mixed generalized survival models (GSMs) with a probit link Royston and Parmar (2002), Liu et al. (2016, 2017); and a mixed version of the linear transformation model with a probit link Hothorn et al. (2018). The class also include heterogeneous types of data such as in Gaussian copulas Guido and Varin (2012, Christoffersen et al. 2021).

For the above models, the marginal likelihood factor for each cluster is commonly written as a GWI when a multivariate normal distribution is assumed for the cluster specific random effects. Typically, the factor for each cluster is intractable but can be approximated using a Laplace approximation Lindstrom and Bates 1990, Wolfinger 1993, Gauss–Hermite quadrature (GHQ), adaptive Gauss–Hermite quadrature (AGHQ) Pinheiro and Bates 1999, or some Monte Carlo (MC) method such as importance sampling. However, an application of a standard result from the generalized skew-normal distribution shows that the marginal likelihood can also, as stated above, be written as a product of multivariate normal CDFs Azzalini 2005, Arnold 2009 or as a mixture of GWIs and CDFs, as has been done for a number of particular models Ochi and Prentice 1984, Pawitan et al. 2004, Guido and Varin 2012, Barrett et al. 2015.

We will refer to approximating the multivariate normal CDFs, rather than the GWIs, as the CDF approach. A large number of algorithms have been developed for the multivariate normal CDF Genz and Bretz 2009 some of which are fast, even for moderate-to-high dimensional integrals. However, these methods are still approximations and, as we will show, the dimension of the CDFs may be much larger than the GWIs in some cases, making the CDF approach less attractive. Nevertheless some researchers have suggested the CDF approach may generally be preferable Barrett et al. 2015.

There are two main contributions in this paper. Firstly, we show how to derive the formulae needed to apply the CDF approach for mixed binomial models, mixed ordinal models, mixed multinomial models, and mixed GSMs. This is done by showing a general
class of models which can be applied in other settings than those we show. Secondly, we study when the CDF approach is preferable and, if not, which method to use for the GWI using simulations studies and an observational data set. In particular, we compare the CDF approach with approximations of the GWI using GHQ, AGHQ, the stochastic spherical-radial rules shown by Genz and Monahan (1998), and a randomized quasi-Monte Carlo (RQMC) method. The particular RQMC method we use is Sobol sequences (Bratley and Fox 1988; Joe and Kuo 2003) using the scrambling method used by Owen (1998). Our simulation studies and application with an observational data set show that none of the approximation methods are uniformly superior to all others.

The software we have written is available at https://github.com/boennecd/mixprobit. It is programmed C++ with our own interface to the third party Fortran code e.g. for the stochastic spherical-radial rules (Genz and Monahan 1999), with some changes to the Fortran code to allow computation in parallel, gradient approximations and more. Parts of the code we have written may already be useful to practitioners as they are, or as components in a procedure.

The structure of the paper is as follows. We introduce the general class of mixed models in Section 2. Section 3 contains a description of the general integral approximation methods we use, along with the approximation we use for the CDF approach. Specific models are shown Section 4. In Section 5, we perform simulation studies where we compare computation times of the approximation methods at a fixed precision level. An application is provided in Section 6, in which we show that the CDF approximation and a MC approximation are fast and yield an improvement compared to a Laplace approximation which is very fast but yields biased estimates as shown by others. We end with a discussion in Section 7. Alternative approximation methods and estimation methods which we do not cover are discussed in Appendix B.

Notation

We denote vectors in lower case with bold font, e.g. \( \mathbf{v} \), and matrices by upper case in bold font, e.g. \( \mathbf{X} \). All scalar functions will be applied element wise. That is, for \( \mathbf{x} = (x_1, x_2)^\top \) then \( f(\mathbf{x}) = (f(x_1), f(x_2))^\top \). This also applies to operators like ‘·’. \( p \) will denote a (conditional) density function or probability mass function. The definition is implicitly given by the context and arguments passed to \( p \).

\( \phi(x; \mu, \sigma^2) \) and \( \Phi(x; \mu, \sigma^2) \) are the probability density function (PDF) and CDF, respectively, for a normal distribution with mean \( \mu \) and standard deviation \( \sigma \). We also define \( \phi(x) = \phi(x; 0, 1) \) and \( \Phi(x) = \Phi(x; 0, 1) \) as shorthands for the standard normal distribution. Further, we define

\[
\Phi^{(k)}(\mathbf{x}; \mu, \Sigma) = \text{P}(\mathbf{X} \leq \mathbf{x}), \quad \mathbf{x} \in \mathbb{R}^k
\]

where \( \mathbf{X} \sim N^{(k)}(\mu, \Sigma) \). \( \phi^{(k)} \) will denote the multivariate normal distribution’s PDF and we will use similar shorthands of \( \phi^{(k)} \) and \( \Phi^{(k)} \) for the standard case. \( \mathbf{0} \) is a vector of zeros and \( \mathbf{1} \) is a vector of ones. The length of the vectors is implicit given by the context to match the vector operations. Similarly, \( \mathbf{I} \) denotes the identity matrix. \( \text{diag}(\cdot) \) returns the diagonal if a single square matrix is passed as the input. \( \text{diag}(\mathbf{A}_1, \ldots, \mathbf{A}_n) \) returns a block diagonal matrix whose block matrices are \( \mathbf{A}_1, \ldots, \mathbf{A}_n \).
2 The Class of Mixed Models

First, we define the general formula for the log marginal likelihood which the mixed models we consider have in common. All the mixed models we use share that the outcomes can be expressed as a transformation of a latent multivariate normal distributed variable. The models have in common that the log marginal likelihood term for each cluster can be written as some function of the outcomes, which has an analytical expression, plus the log of a GWI or multivariate normal CDF. To be specific, let \( y_i = (y_{i1}, \ldots, y_{in})^T \) denote the \( n_i \) observed outcomes for cluster \( i \). Let \( U_i \in \mathbb{R}^K \) denote unobserved cluster specific random effects, and let \( \Sigma \) and \( \theta \) be unknown model parameters. Then the complete data likelihood factor for the \( i \)th group is

\[
p(u_i, y_i) = c_i(y_i; \Sigma, \theta) \phi^{(K)}(u_i; \mu_i(y_i), \Sigma) h_i(y_i, u_i, \theta)
\]

where \( c_i, \mu_i, \) and \( h_i \) have an analytical expression and are easy to evaluate for a given \( u_i \). It then follows that the log marginal likelihood term is

\[
l_i(\theta, \Sigma) = \log c_i(y_i; \Sigma, \theta) + \log \int \phi^{(K)}(u; \mu_i(y_i), \Sigma) h_i(y_i, u, \theta) \, du
\]

which is the log of some function with an analytical expression, \( c_i \), plus the log of a GWI. The log marginal likelihood given \( i = 1, \ldots, G \) groups is

\[
\sum_{i=1}^G l_i(\theta, \Sigma)
\]

In what follows, we drop the cluster index, \( i \), to ease the notation. We only need to derive the log marginal likelihood for a single group or the complete data likelihood for a single group in order to get the log marginal likelihood in Equation (3). Thus, we will e.g. write \( y \) when we implicitly mean \( y_i \) for some \( i \).

What is particular for the models that we consider is that we can also write the complete data likelihood as

\[
p(u, y) = c(y; \Sigma, \theta) \phi^{(K)}(u; \mu(y), \Sigma) \Phi^{(k(y))}(\eta(y, \theta) + Z(y)u; 0, \Omega)
\]

where \( k(y), \eta(y, \theta), Z(y), \) and \( \Omega \) are known and may be specific to the cluster. Thus, the log marginal likelihood term can also be written as

\[
l(\theta, \Sigma) = \log c(y; \Sigma, \theta) + \log \int \phi^{(K)}(u; \mu(y), \Sigma) \Phi^{(k(y))}(\eta(y, \theta) + Z(y)u; 0, \Omega) \, du
\]

where it is computationally advantage to use that when \( k(y) < K \)

\[
\int \phi^{(K)}(u; \mu(y), \Sigma) \Phi^{(k(y))}(\eta(y, \theta) + Z(y)u; 0, \Omega) \, du
= \int \phi^{(k(y))}(u; Z(y)\mu(y), Z(y)\Sigma Z(y)^\top) \Phi^{(k(y))}(\eta(y, \theta) + u; 0, \Omega) \, du
\]

We will now show that the intractable integral in the above log marginal likelihood term can be expressed as the log of a GWI, as it is now, or as the log of a multivariate normal CDF. The latter turns out to be advantageous as it may be preferable to approximate the CDF rather than the GWI in some cases, as our simulation examples show in Section 5.
2.1 Generalization of the Skew-normal Distribution

We will need a few results from a generalization of the multivariate skew-normal distribution in order to derive an alternative expression for the log marginal likelihood and the conditional density of the random effects given the observed outcomes. These are stated in Azzalini (2005); Arnold (2009). Consider two random vectors $V_1$ and $V_2$ such that

$$
\begin{pmatrix} V_1 \\ V_2 \end{pmatrix} \sim N^{(k_1+k_2)} \left( \begin{pmatrix} \xi_1 \\ \xi_2 \end{pmatrix}, \begin{pmatrix} \Xi_{11} & \Xi_{12} \\ \Xi_{21} & \Xi_{22} \end{pmatrix} \right)
$$

(7)

where $V_1 \in \mathbb{R}^{k_1}$ and $V_2 \in \mathbb{R}^{k_2}$, $\xi_1$ and $\xi_2$ are mean vectors for $V_1$ and $V_2$, respectively, and $\Xi$ is a covariance matrix which we have decomposed into four parts. Then the joint density of $V_1 = v_1$ and $V_2 \leq v_2$ is

$$
\phi^{(k_1)}(v_1; \xi_1, \Xi_{11}) P(V_2 < v_2 \mid V_1 = v_1) = \phi^{(k_1)}(v_1; \xi_1, \Xi_{11}) \phi^{(k_2)}(v_2 - \Xi_{21}\Xi_{11}^{-1}(v_1 - \xi_1); \xi_2, \Xi_{22} - \Xi_{21}\Xi_{11}^{-1}\Xi_{12})
$$

(8)

and the marginal for $P(V_2 \leq v_2)$ is

$$
P(V_2 \leq v_2) = \phi^{(k_2)}(v_2; \xi_2, \Xi_{22}) = \Phi^{(k_2)}(0; \xi_2 - v_2, \Xi_{22})
$$

(9)

$$
= \int \phi^{(k_1)}(v_1; \xi_1, \Xi_{11}) P(V_2 < v_2 \mid V_1 = v_1) \, dv_1
$$

(10)

Both the integral in Equation (9), the CDF, and the integral in Equation (10), the GWI, are intractable but their dimensions may differ greatly. Notice that the integrand in Equation (10) match the integrand in Equation (5). Thus, we can use the identity in Equation (9) and (10) to express the $K$-dimensional GWI in the log marginal likelihood term as a $k(y)$-dimensional multivariate normal CDF. Specifically, we find that

$$
\begin{align*}
\xi_1 &= \mu(y) \\
\Xi_{22} &= \Omega + Z(y)\Sigma Z(y)^\top \\
\Xi_{11} &= \Sigma \\
\Xi_{21} &= -Z(y)\Sigma \\
k_1 &= K \\
k_2 &= k(y) \\
v_2 &= \eta(y, \theta) - \Xi_{21}\Xi_{11}^{-1}\mu(y)
\end{align*}
$$

Thus, the log marginal likelihood in Equation (5) can be expressed as

$$
l(\theta, \Sigma) = \log c(y; \Sigma, \theta) + \log \int \phi^{(K)}(u; \mu(y), \Sigma) \Phi^{(k(y))}(\eta(y, \theta) + Z(y)u; 0, \Omega) \, du
$$

$$
= \log c(y; \Sigma, \theta) + \log \Phi^{(k(y))}(0; -\eta(y, \theta) - Z(y)\mu(y), \Omega + Z(y)\Sigma Z(y)^\top)
$$

Importantly, numerically approximating the CDF of a multivariate normal distribution, and its derivatives with respect to the mean and covariance matrix, have received a great deal of attention. We discuss the particular approximations we use in Section 3. It is important to be clear that the CDF approach to fitting mixed models with probit links is an approximation method. We would argue that some authors have not been clear about this. Barrett et al. (2015), for example, state that the multivariate normal CDF has a closed form solution and thus, using the CDF in Equation (9) results in exact likelihood inference. However, the CDF of a multivariate normal distribution over a hyperrectangle has no analytical solution in general, and as our simulation example in Section 5 shows, it seems that, unlike what is
implied by these authors, it is not always preferable to use the CDF approach, as opposed to the GWI approach with efficient C++ and Fortran implementations, or vice-versa.

The conditional density of \( V_1 \) given \( V_2 \leq v_2 \) is identical to the density of a generalized skew-normal distribution. The conditional density is given by

\[
p(v_1 | V_2 \leq v_2) = \phi^{(k_1)}(v_1; \xi_1, \Xi_{11}) \frac{P(V_2 \leq v_2 | V_1 = v_1)}{P(V_2 \leq v_2)}
\]

which is equivalent to the conditional density of the random effects given the outcomes for the class of mixed models we work with. A random variable follows a generalized skew-normal distribution if its density is given by (11) where \( v_2, \xi_1, \xi_2, \Xi_{12} = \Xi_{21}^T, \) and \( \Xi_{22} \) are parameters in the family. We now turn to the approximation method we use in the CDF approach and the general integral approximation methods we consider to approximate the GWI.

### 3 Approximation Methods for Mixed Effects Models with Probit Link Functions

In this section we describe the approximation methods that we use. We start with the CDF approach where we approximate the CDF rather than the GWI. As mentioned previously, approximating the multivariate normal CDF has received a great deal of attention. The approach of Genz (1992), or the similarly and seemingly independently developed Geweke-Hajivassiliou-Keane simulator (GHK) used by Hajivassiliou et al. (1996), is fast and quite precise. Moreover, the implementation in the \texttt{mvtnorm} package (Genz and Bretz 2009, Genz et al., 2020) in R (R Core Team, 2019) uses randomized Korobov rules (Niederreiter, 1972; Keast, 1973; Cranley and Patterson, 1976) which yields a huge reduction in computation time compared to the MC implementation of the method described in Genz (1992). Thus, the CDF approximation we are using is also a RQMC method (Section 3.1.4). We note that we have adapted the Fortran code for the CDF approximation to also provide gradient approximations with respect to the mean and covariance matrix. This resulted in a more than four-fold reduction in the computation time in the example in Section 6. See Hajivassiliou et al. (1996) for a thorough comparison of methods to approximate the multivariate normal CDF and its derivatives.

The method suggested by Genz (1992) works as follows. Let \( \Sigma = SS^T \) where \( S \) is the Cholesky decomposition of \( \Sigma \). Then

\[
\Phi^{(k)}(l, b; \mu, \Sigma) = \int_{l_1}^{b_1} \cdots \int_{l_k}^{b_k} \phi^{(k)}(v; \mu, \Sigma) \, dv_1 \cdots dv_k
\]

\[
= \int_{l_1}^{b_1} \cdots \int_{l_k}^{b_k} \phi(v_1, \ldots, v_k) \, dv_1 \cdots dv_k
\]

\[
= \int_{l_1}^{b_1} \phi(v_1) \int_{l_2(v_1)}^{b_2(v_1)} \phi(v_2) \cdots \int_{l_k(v_1, \ldots, v_{k-1})}^{b_k(v_1, \ldots, v_{k-1})} \phi(v_k) \, dv_1 \cdots dv_k
\]
where
\[
\tilde{l}_1 = s_{11}^{-1}(l_1 - \mu_1) \quad \tilde{l}_k(v_1, \ldots, v_{k-1}) = s_{kk}^{-1}\left(l_k - \mu_k - \sum_{i=1}^{k-1} s_{ki}v_i\right)
\]
\[
\tilde{b}_1 = s_{11}^{-1}(u_1 - \mu_1) \quad \tilde{b}_k(v_1, \ldots, v_{k-1}) = s_{kk}^{-1}\left(b_k - \mu_k - \sum_{i=1}^{k-1} s_{ki}v_i\right)
\]

This suggests the following MC estimator: sample \(\hat{v}_1\) from a truncated normal distribution truncated at \(\tilde{l}_1\) and \(\tilde{b}_1\). Then sample \(\hat{v}_2\) from truncated normal distribution truncated at \(\tilde{l}_2(\hat{v}_1)\) and \(\tilde{b}_2(\hat{v}_1)\). Repeat sampling till reaching \(\hat{v}_{k-1}\). Then evaluate
\[
(\Phi(\tilde{b}_1) - \Phi(\tilde{l}_1)) \prod_{i=2}^{k} \left(\Phi(\tilde{b}_i(\hat{v}_1, \ldots, \hat{v}_{i-1})) - \Phi(\tilde{l}_i(\hat{v}_1, \ldots, \hat{v}_{i-1}))\right)
\] (12)

Repeat for a new sample and average the results till the estimated MC error is below a prespecified threshold. A greedy variable reordering either to increase the expected width of the inner most integrals or to reduce the variance of Equation (12) can yield a substantial reduction in variance at a fixed number of samples in some cases (Genz and Bretz, 2009, Section 4.1).

Because of the aforementioned method and its precision, approximating the \(k_2\)-dimensional CDF might be attractive even when \(k_2\) is larger than \(k_1\). However, it should be noticed that if \(k_1\) is much smaller than \(k_2\), then approximating the GWI in Equation (10) may be more attractive than approximating the CDF in Equation (9), as we will show in Section 5. For the models described in this paper, \(k_1 = K\) and \(k_2 = k(y)\). Only the latter is model specific.

### 3.1 Approximating the Gaussian Weighted Integral

We now focus on approximating the GWI. That is, integrals of the form
\[
g(u) = \phi^{(k_1)}(u; \xi_1, \Xi_{11}) P(V_2 < v_2 | V_1 = u)
\]
\[
L = \int g(u) \, du
\] (13) (14)

where we let \(g(u)\) denote the integrand and \(P(V_2 < v_2 | V_1 = u)\) is a \(k_2\)-dimensional CDF as in Equation (8).

It is worth remarking that the structure of the conditional CDF, \(P(V_2 < v_2 | V_1 = u)\), should be used for a given model; for example, this expression can be evaluated as products of powers of \(n\) CDFs of the standard normal distribution in the mixed binomial model we cover later. This is much more attractive than approximating the \(k_2\)-dimensional conditional CDF in the integrand as a general CDF. Moreover, special structure may be exploited in certain cases as done by Ochi and Prentice (1984). Because of the special structure, approximating the GWI may be faster than approximating the CDF at a fixed precision. Lastly, Equation (6) should be used when \(k(y) < K\).
3.1.1 Laplace Approximation

One way to approximate the GWI is to use a Laplace approximation. This begins with computing a mode 
\[ \hat{u} = \arg \max_u \log g(u) \]
and the Hessian 
\[ \hat{H} = \left. \frac{\partial^2}{\partial u \partial u^\top} \log g(u) \right|_{u=\hat{u}} \]
The Laplace approximation is then 
\[ \int g(u) \, du \approx \frac{(2\pi)^{K/2}}{|-\hat{H}|^{1/2}} g(\hat{u}) \]
Lindstrom and Bates (1990) and Wolfinger (1993) show a version of the Laplace approximation in which fixed effects are also estimated. The Laplace approximation is a very fast means of approximating the log marginal likelihood, but may have a substantial bias in some cases (Raudenbush et al., 2000; Pinheiro and Chao, 2006; Joe, 2008). The computational complexity is \( O(K^3 + nK) \) if we assume that the \( K \)-dimensional mode can be estimated at rate, at or below, \( O(K^3 + nK) \).

3.1.2 Simple Monte Carlo Estimator

For the simulations, our ground truth estimator will be a simple MC estimator where we use a large number of samples. A simple procedure for approximating the marginal likelihood in Equation (14) is to sample \( u \sim N(k_1)(\hat{\xi}, \hat{\Xi}) \), evaluate \( P(V_2 < v_2 | V_1 = u) \), and average the outcomes. An adaptive and yet still simple alternative, is to compute \( \hat{u} \) and \( \hat{H} \) as we do with the Laplace approximation. Then letting 
\[ \tilde{g}(u) = \phi^{(k_1)}(u; \hat{u}, (-\hat{H})^{-1}) \frac{\phi^{(k_1)}(u; \hat{\xi}, \hat{\Xi})}{\phi^{(k_1)}(\hat{u}; \hat{\xi}, \hat{\Xi})} P(V_2 < v_2 | V_1 = u), \quad (15) \]
we perform importance sampling by sampling \( u \sim N^{(k_1)}(\hat{u}, (-\hat{H})^{-1}) \), evaluating the rest of the factors in the integrand \( \tilde{g} \), and averaging the outcomes. The additional computation cost of finding the mode, computing the Hessian, and the overhead in the integrand is typically much smaller compared to the reduction in the variance of the estimator.

Our C++ implementation also uses three simple antithetic variables for each sampled \( u \) to reduce the variance of the estimator. These are the so-called location and scale balanced variables in the terminology of Durbin and Koopman (1997). A major advantage of this MC estimator and all the other MC estimators that we discuss is that a standard error of the estimator can easily be computed at any iteration of the approximation. Thus, a stopping criteria can be implemented, as is done in the CDF approximation in the mvtnorm package.
Figure 1: The illustration compares MC with QMC. All three figures show 512 points. The left figure shows points sampled from the uniform distribution over $[0, 1)^2$. The figure in the middle shows the first two dimensions from a Sobol sequence and the right figure shows the 20th and 33rd dimensions. Darker colors come later in the sequences to show that points from the Sobol sequence tends to be further apart if they are closer to each other in the sequence.

### 3.1.3 Alternative Monte Carlo Estimator

The variance of the importance sample estimator at a fixed computing budget may still be unacceptable. Thus, we will use the RANRTH Fortran subroutine developed by Genz and Monahan (1999) as an alternative MC estimator. This subroutine uses stochastic spherical-radial rules to approximate GWIs like Equation (14). The degree one rule is identical to using the location balanced variables that we use with our importance sampler. Genz and Monahan (1999) show higher degree rules. We will use the five degree rule. We changed the implemented Householder reflection to use the algorithm shown in Golub and Van Loan (2013, Section 5.1). The previous algorithm is numerically unstable and caused problems in our simulations.

Let $s$ be the number of samples that is used. Then the complexity is $O(K^3 + s(nK + K^2))$ with the rule that we use. As we show later, using an adaptive approach as suggested by Genz and Monahan (1998), similar to what we do with the importance sampler in Section 3.1.2 yields much more precise results at a fixed computing budget. Our main reason to include the method suggested by Genz and Monahan (1999) is not to argue to use this particular MC estimator but to show one MC estimator of the GWI which may scale better in the number of random effect terms, $K$, than the GHQ and AGHQ approaches which we cover in Section 3.1.5.

### 3.1.4 Randomized Quasi-Monte Carlo

MC methods have a $O(s^{-1/2})$ convergence rate of the estimator where $s$ is the number of samples. This can make it very expensive to achieve a given accuracy. An alternative is to consider quasi-Monte Carlo (QMC) methods. QMC methods have an error bound which is $O(s^{-1}(\log s)^K)$ but the convergence rate is often lower in practical applications. QMC
methods achieve a better convergence rate by selecting a sequence of points in \([0, 1)^K\) which is more uniformly spread than a random sequence. We illustrate this in Figure 1 where we sample uniformly from \([0, 1)^K\) and compare the sample with the Sobol sequence. The uniformity is measured by a sequence’s discrepancy which can be used to bound the error with the Koksma–Hlawka inequality (Caflisch, 1998).

We use RQMC and particularly scrambled Sobol sequences with the scrambling method used by Owen (1998). The Fortran code is from the randtoolbox package (Christophe and Petr, 2020) and is based on the code implemented by Bratley and Fox (1988) and Joe and Kuo (2003). One advantage of RQMC is that we can get a standard error for the estimate. This has allowed us to implement a stopping criteria similar to that available with the MC methods we use. We have also used an adaptive procedure with RQMC. We transform the \([0, 1)^K\) samples, first by applying the inverse standard normal CDF elementwise, as we do with our MC methods. However, we then multiply by \(Q\Lambda^{1/2}\), where \((-H)^{-1} = Q\Lambda Q^\top\) is the eigendecomposition rather than a Cholesky decomposition of \((-H)^{-1}\). The motivation is that the low-dimensional projections obtained by grouping coordinates of the Sobol sequence that we use, do not have holes for a small number of samples with the leading dimensions, although with the later dimensions they do, as shown in Figure 1 (Morokoff and Caflisch, 1994). Thus, we ensure that the first dimensions have roughly the highest variation of the integrand by using \(Q\Lambda^{1/2}\) and these do not have holes.

### 3.1.5 Gauss–Hermite Quadrature

In some cases, it may be preferable to use some deterministic approximation, such as using some type of quadrature, for the GWI in Equation (14), when \(K\) is small. In particular, GHQ and AGHQ are often used (Liu and Pierce, 1994; Pinheiro and Bates, 1995). An application of GHQ involves change-of-variables such that the integrand is

\[
\phi^{(k_1)}(u; 0, 2I) P \left( V_2 < v_2 \mid V_1 = \xi_1 + \sqrt{2\Xi^{1/2}u} \right),
\]

where \(\Xi^{1/2}\) is a Cholesky decomposition of \(\Xi\) such that \(\Xi = \Xi^{1/2}\Xi^{1/2}\). Direct application of GHQ is then applicable to each of the \(K\) random effect terms. This implies \(b\) values for each of the \(K\) random effect terms, resulting in \(b^K\) so-called nodes at which the integrand is evaluated. Thus, the computational complexity is \(O((K^2 + nK)b^K)\).

Using an adaptive procedure such as suggested by Pinheiro and Bates (1995) involves a similar application of GHQ but for the integral whose integrand is shown in Equation (15). This may require substantially fewer nodes, \(b^K\), and result in much faster computation times at a fixed precision (Pinheiro and Bates, 1995; Rabe-Hesketh et al., 2002), as is the case in the simulation example we provide in Section 5. While both GHQ and AGHQ may be fast for few random effect terms, i.e. small \(K\), they will be expensive even for few values for each random effect term, \(b\), when there are many random effect terms.

### 4 Models

In this section we show some mixed effects models which are within the class of models introduced in Section 2. The formulae are provided to apply the CDF approach.
4.1 Mixed Probit Model

The first model we consider is the mixed probit model for binomial outcomes. Assume that we observe counts \( Y \in \{0, \ldots, m\}^n \) for all individuals \( i = 1, \ldots, n \) and observe a fixed effect design matrix \( X = (x_1, \ldots, x_n)\top \) and random effect design matrix \( Z = (z_1, \ldots, z_n)\top \). \( Y \) can be generalized to non-equal counts such that \( Y \in \{0, \ldots, m_1\} \times \cdots \times \{0, \ldots, m_n\} \).

Moreover, we assume that there is an unobserved random effect \( U \in \mathbb{R}^K \). The elements of \( Y \) are assumed to be independent conditional on the random effect. Let \( \beta \) be a coefficient vector and let Bin denote the binomial distribution such that if \( V \sim \text{Bin}(q, k) \) then

\[
p(v) = \binom{k}{v} q^v (1 - q)^{k-v}
\]

We assume that the conditional distribution of each element of \( Y \) is \( Y_i | U = u \sim \text{Bin}(\Phi(x_i\top \beta + z_i\top u), m) \).

That is, we are considering a generalized linear mixed model (GLMM) with a probit link function. Further, we assume that the random effects follow a multivariate normal distribution such that \( U \sim N^K(0, \Sigma) \).

The complete data likelihood is therefore

\[
p(u, y) = \phi^K(u; 0, \Sigma) \prod_{i=1}^n \left( \frac{m}{y_i} \right) \Phi(x_i\top \beta + z_i\top u)^{y_i} (1 - \Phi(x_i\top \beta + z_i\top u))^{m-y_i}
\]

\[
= c(y) \phi^K(u; 0, \Sigma) \prod_{i=1}^n \Phi(x_i\top \beta + z_i\top u)^{y_i} \Phi(-x_i\top \beta - z_i\top u)^{m-y_i}, \tag{16}
\]

where

\[
c(y) = \prod_{i=1}^n \left( \frac{m}{y_i} \right)
\]

and the log marginal likelihood is

\[
l(\beta, \Sigma) = \log p(y) = \log \int p(u, y) \, du, \tag{17}
\]

which is needed for model estimation in a frequentist analysis.

We will define a few augmented matrices in order to show a form of the complete data likelihood shown in Equation (16) which is similar to Equation (4). Let

\[
\tilde{X}_i = (x_1, \ldots, x_i, -x_i, \ldots, -x_i)\top
\]

\[
= (1, \ldots, 1, -1, \ldots, -1)\top x_i\top = j_i x_i\top
\]

\[
\tilde{X} = (\tilde{X}_1, \ldots, \tilde{X}_n)\top = \begin{bmatrix}
  j_1 & 0 & \cdots & 0 \\
  0 & j_2 & \cdots & 0 \\
  \vdots & \ddots & \ddots & \vdots \\
  0 & \cdots & 0 & j_n
\end{bmatrix} X = JX \tag{18}
\]
We define $\tilde{Z}_i$ and $\tilde{Z}$, similarly. We can now rewrite the complete data likelihood as

$$p(u, y) = c(y) \phi(K)(u; 0, \Sigma) \prod_{i=1}^{n} \Phi^{(m)}(\tilde{X}_i \beta + \tilde{Z}_i u)$$

and the log marginal likelihood as

$$l(\beta, \Sigma) = \log \int p(u, y) \, du$$

$$= \log c(y) + \log \int \phi(K)(u; 0, \Sigma) \Phi^{(nm)}(\tilde{X} \beta + \tilde{Z} u) \, du$$

In order to find the formula needed to apply the CDF approach, it follows from Equation (20) that

$$\xi_1 = 0 \quad \xi_2 = 0 \quad \Xi_{11} = \Sigma \quad \Xi_{21} = -\tilde{Z} \Sigma$$

$$\Xi_{22} = I + \tilde{Z} \Sigma \tilde{Z}^T \quad k_1 = K \quad k_2 = nm \quad v_2 = \tilde{X} \beta$$

Notice that $k_2 = n$ in the binary case, $m = 1$, implying that the CDF approach seems advantageous particularly in the binary case. As an example, [Pawitan et al. (2004) and Lichtenstein et al. (2009)] use the CDF approach to estimate a model for binary traits with family data. In this setting, the CDF approach is very attractive as $K = n$ such that $k_2 = k_1$.

The random effect vector, $U$, contains the random effect for a given cluster where all observations are only assumed independent given this unobserved variable. Thus, $K$ is the number of random effect terms that we have to integrate out. This can be defined both in a crossed random effects setup and in a nested random effect setup. As an example of nested random effects, let each cluster be a school with six classes and suppose that we include both a school specific random effect and a class specific random effect. Then $K = 7$, since there is a total of 7 random effect terms. We provide an application with a crossed random effects setup in Section 6 with $K = 20$.

### 4.2 Multinomial Probit Regression

The second model that we consider is a multinomial probit model in which each observed outcome, $Y_i$, can fall into one of $c$ categories. Let $Y \in \{1, \ldots, c\}^n$ denote a vector of observed outcomes, $Z_i = (z_{i1}, \ldots, z_{ic})^T \in \mathbb{R}^{c \times K}$ be a matrix of known random effect covariates for each of the $c$ categories for individual $i$, $x_i$ be a vector of known fixed effect covariates for individual $i$, $B = (\beta_1, \ldots, \beta_c)^T$ be a matrix of fixed effect coefficients, and

$$A_i \mid U = u \sim N(B x_i + Z_i u, I)$$

be the vector of latent variables for individual $i$ such that

$$Y_i = k \iff \forall k \neq k' : A_{ik} > A_{ik'}, \quad k, k' \in \{1, \ldots, c\}.$$
Let \( \mathbf{B}_{(-k)} = (\beta_1, \ldots, \beta_{k-1}, \beta_{k+1}, \ldots, \beta_c) \) be the coefficient matrix without the \( k \)th row and similarly define \( \mathbf{Z}_{i(-k)} \). It then follows that the conditional probability of \( Y_i \) falling into the \( k \)th category, given the random effect, \( U \), is

\[
P(Y_i = k \mid U = u) = \int_{\mathcal{C}_{ik}} \phi(c)(a; \mathbf{B}x_i + \mathbf{Z}_i u, \mathbf{I}) \, da
\]

\[
= \int \phi(a_k; \beta_k^\top x_i + z_{ik}^\top u, 1) \left( \prod_{k' \neq k}^{\alpha_k} \int_{-\infty}^{\alpha_{k'}} \phi(a_{k'}; \beta_{k'}^\top x_i + z_{ik'}^\top u, 1) \, da_{k'} \right) \, da_k
\]

\[
= \int \phi(a_k; \beta_k^\top x_i + z_{ik}^\top u, 1) \Phi(c-1)(1a_k - \mathbf{B}_{(-k)}x_i - \mathbf{Z}_{i(-k)}u) \, da_k
\]

\[
= \Phi(c-1)((1\beta_k^\top - \mathbf{B}_{(-k)}) x_i + (1z_{ik}^\top - \mathbf{Z}_{i(-k)}) u; 0, \mathbf{I} + 11^\top)
\]

where the last equality follows from the identity in Equation (10). See McFadden (1984) for a similar derivation. Thus, the complete data likelihood is

\[
p(u, y) = \phi(K)(u; 0, \Sigma) \prod_{i=1}^{n} \Phi(c-1)(\tilde{\mathbf{B}}_{yi}, x_i + \tilde{\mathbf{Z}}_{iy} u; 0, \mathbf{I} + 11^\top)
\]

To get Equation (22) into a form like in Equation (4), let \( \tilde{\mathbf{B}} = \text{diag}(\tilde{\mathbf{B}}_{y_1}, \ldots, \tilde{\mathbf{B}}_{y_n}) \), \( \mathbf{x} = (x_1^\top, \ldots, x_n^\top)^\top \), and \( \mathbf{Z} = (\tilde{\mathbf{Z}}_{1y_1}^\top, \ldots, \tilde{\mathbf{Z}}_{ny_n}^\top)^\top \). Then the complete data likelihood can be written as

\[
p(u, y) = \phi(K)(u; 0, \Sigma) \Phi(n(c-1))(\tilde{\mathbf{B}}x + \tilde{\mathbf{Z}}u; 0, \text{diag}(\mathbf{I} + 11^\top, \ldots, \mathbf{I} + 11^\top)).
\]

Thus, we find that

\[
\xi_1 = 0 \quad \xi_2 = 0 \quad \Xi_{11} = \Sigma \quad \Xi_{21} = -\tilde{\mathbf{Z}}\Sigma \n
\Xi_{22} = \Omega + \tilde{\mathbf{Z}}\Sigma\tilde{\mathbf{Z}}^\top \quad k_1 = K \quad k_2 = n(c-1) \quad \nu_2 = \tilde{\mathbf{B}}x
\]

with

\[
\Omega = \text{diag}(\mathbf{I} + 11^\top, \ldots, \mathbf{I} + 11^\top),
\]

Notice that the CDF in Equation (23) is of dimension \( n(c-1) \) whereas the dimension of the CDF in Equation (19) is \( nm \). As we will show later, the dimension of the CDF is important in terms of which approximation becomes preferable.
4.2.1 Ordered Case

Assume instead that the $c$ categories are ordered and let $\gamma = (\gamma_0, \ldots, \gamma_c)^T = (-\infty, \gamma_1, \ldots, \gamma_{c-1}, \infty)^T$ be an unknown vector of bin boundary parameters. Let $A_i$ be an unknown latent variable for the $i$th individual and let

$$A_i \mid U = u \sim N(x_i^T \beta + z_i^T u, 1)$$

$$Y_i = k \Leftrightarrow \gamma_{k-1} < A_i \leq \gamma_k.$$ 

Then the complete data likelihood is

$$p(u, y) = \phi^{(K)}(u; 0, \Sigma) \prod_{i=1}^n (\Phi(\gamma_{y_i} - x_i^T \beta - z_i^T u) - \Phi(\gamma_{y_i-1} - x_i^T \beta - z_i^T u))$$ (24)

However, we cannot rewrite Equation (24) into an expression like in Equation (4).

Though, define

$$\Phi^{(k)}(l, b; \mu, \Sigma) = P(l < X \leq b), \quad X \sim N^{(k)}(\mu, \Sigma),$$

$$g(k) = \gamma_k, \quad X = (x_1, \ldots, x_n)^T, \quad \text{and} \quad Z = (z_1, \ldots, z_n)^T.$$ 

Then the complete data likelihood can be written as

$$p(u, y) = \phi^{(K)}(u; 0, \Sigma) \Phi^{(n)}(g(y - 1) - X\beta - Zu, g(y) - X\beta - Zu)$$

This turns out also to give an alternative expression of the log marginal likelihood which is the log of a multivariate normal CDF. To see this, let

$$P(l < V_2 \leq b \mid V_1 = v_1) = \Phi^{(k_2)}(l - \Xi_{21}\Xi_{11}^{-1}(v_1 - \xi_1), b - \Xi_{21}\Xi_{11}^{-1}(v_1 - \xi_1); \xi_2, \Xi_{22} - \Xi_{21}\Xi_{11}^{-1}\Xi_{12})$$ (25)

to show that

$$P(l < V_2 \leq b) = \Phi^{(k_2)}(l, b; \xi_2, \Xi_{22})$$

$$= \int \phi^{(k_1)}(v_1; \xi_1, \Xi_{11}) P(l < V_2 \leq b \mid V_1 = v_1) \, dv_1.$$ 

This shows that we also have a choice between a CDF and a GWI for the mixed ordered multinomial model by setting

$$\xi_1 = 0 \quad \xi_2 = 0 \quad \Xi_{11} = \Sigma \quad \Xi_{21} = Z\Sigma \quad \Xi_{22} = I + Z\Sigma Z^\top$$

$$b = g(y) - X\beta.$$ 

Lastly, if we add an identification constraint of $\gamma_1 = 0$, it reduces to the mixed binomial model in the binary case, $m = 1$, if $c = 2$. Moreover, $k_2 = n$ like in the mixed binomial model in the binary case and, importantly, this is independent of the number of categories, $c$. 

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4.3 Generalized Survival Models

Related classes of models are the mixed GSM with a probit link function [Royston and Parmar, 2002; Liu et al., 2016, 2017] and the mixed version of the linear transformation model (described by Hothorn et al., 2018). For modelling time to events for \( i = 1, \ldots, n \) individuals, we let \( T_i^* \) be the \( i \)th individual’s survival time. Further, we assume independent censoring times denoted by \( C_i \) such that we only observe \( T_i = \min(T_i^*, C_i) \). We define the event indicator \( D_i = 1_{(T_i^* < C_i)} \). \( D_i \) takes value one if the event of the \( i \)th individual is observed. We let \( S(t \mid x, z, u) = P(T^* > t \mid x, z, u) \) denote the conditional survival function given the fixed effect covariates, \( x \), the random effect covariates, \( z \), and the random effect, \( u \).

In a GSM the conditional survival function, \( S(t \mid x, z, u) \), is modelled on some link scale defined by a link function \( g \). We assume that \( g = -\Phi^{-1} \) such that

\[-\Phi^{-1}(S(t \mid x, z, u)) = -\Phi^{-1}(S_0(t)) + x^\top \beta + z^\top u\]

for some baseline survival function \( S_0 \). While the above form is instructive, we typically model \( -\Phi^{-1}(S_0(t)) \) by a dot product between some spline basis over time and a coefficient vector. This can be generalized to

\[-\Phi^{-1}(S(t \mid x, z, u)) = x^\top(t)\beta + z^\top u\]

to allow for some time-varying design vector \( x(t) \in \mathbb{R}^d \), i.e. to allow for time-varying fixed effects. Though, it is important to keep in mind that a monotonicity constraint should be placed on \( x(t)^\top \beta \) since the survival probability needs to decrease as a function of time. This often is not an issue when there is only a time-varying intercept in which case the constraint can be handled e.g. with an I-splines or a relaxation.

In order to show the complete data likelihood, we let \( \mathcal{C} = \{ i \in \{1, \ldots, n \} : d_i = 0 \} \) denote the set of indices of the individuals with a censored event time. Similarly, let \( \mathcal{O} \) denote the set of indices of the individuals with an observed event time. Further, let \( x_j(t) = (x_{j1}(t), \ldots, x_{jd}(t))^\top \) denote the derivative of the fixed effect covariates with respect to time and \( X^o(T^o) = (x_{j1}(T_j))_{j \in \mathcal{O}}^\top \) be the design matrix for the individuals with an observed event time and similarly define \( X^{o+c}(T^o) = (x_{j1}(T_j))_{j \in \mathcal{O} \cup \mathcal{C}}^\top, Z^o, T^o, X^c(T^o), Z^c, \) and \( T^c \) where the latter three are for censored individuals. Lastly, let \( n_o = |\mathcal{O}| \) denote the number of observed events and \( n_c = |\mathcal{C}| \) denote the number of censored events. Then the complete data likelihood is

\[ \phi^{(K)}(u; 0, \Sigma)c(t^o, X^o, \beta)\phi^{(n_o)}(-X^o(t^o)\beta - Z^o u)\phi^{(n_c)}(-X^c(t^c)\beta - Z^c u) \]  

(26)

where \( c(t^o, X^o, \beta) = -X^{o+c}(t^o)\beta \). Further, \( c(t^o, X^o, \beta) = 1 \) and \( \phi^{(n_o)}(-X^o(t^o)\beta - Z^o u) = 1 \) if \( n_o = 0 \) and \( \phi^{(n_c)}(-X^c(t^c)\beta - Z^c u) = 1 \) if \( n_c = 0 \) by definition. We can simplify the log marginal likelihood, \( l(\beta, \Sigma) \), first by defining

\[ H(t^o, Z^o, \Sigma) = H = Z^o\top Z^o + \Sigma^{-1} \]
\[ h(t^o, X^o, Z^o, \Sigma) = h = H^{-1}Z^o\top(-X^o(t^o)\beta) \]
\[ k(t^o, X^o, Z^o, \Sigma) = c(t^o, X^o, \beta)(2\pi)^{-n_o/2} |\Sigma H|^{-1/2} \]
\[ \cdot \exp \left( -\frac{1}{2}(-X^o\beta(t^o))^\top(-X^o\beta(t^o)) + \frac{1}{2}h^\top H h \right) \]

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and we set $H = \Sigma^{-1}$, $h = 0$, and $k(t^o, X^o, Z^o, \Sigma) = c(t^o, X^o, \beta)$ if $\mathcal{O} = \emptyset$. Then, we can write the log marginal likelihood as

$$l(\beta, \Sigma) = \log k(t^o, X^o, Z^o, \Sigma) + \log \int \phi^{(K)}(u; h, H^{-1}) \Phi^{(nc)}(-X^c(t^c)\beta - Z^c u) \, du$$

which is in the same form as the log marginal likelihood in Equation (5). One can observe that a mixed Tobit model is also within this class if we set $x_j(t) = (-t, x_{j1}, \ldots, x_{jl})^\top$ and allow for a known offset. Expressed another way, the GSM can be seen as a generalization of the Tobit model when a probit link is applied.

To apply the CDF approach, we can use Equation (27) and Equation (10) to show that

$$\xi_1 = h \quad \xi_2 = 0 \quad \Xi_{11} = H^{-1} \quad \Xi_{21} = Z^c H^{-1}$$

Notice that the dimension of the CDF in the CDF approach is equal to the number of censored individuals, $n_c$, making this approach very attractive when there are few censored individuals.

We will not show more examples of mixed models for which the log marginal likelihood can be written in the form as for Equation (5). We will mention, however, that the joint model of repeated measures and time to event data with the discrete hazard survival submodel described by Barrett et al. (2015), can be derived by using the results from the mixed binomial model in Section 4.1 in the binary case, $m = 1$, along with similar arguments as we use above to get from the complete data likelihood in Equation (26) to the log marginal likelihood in Equation (27).

5 Simulation Study

We now present a simulation where we study computation times for approximating a log marginal likelihood term for the mixed binomial model with a single, $m = 1$, binary outcome. We are particularly interested in the computation cost as a function of the number of observations, $n$, in a cluster and the number of random effect terms, $K$. For the calculations, we determine a priori the number of nodes to use with (adaptive) GHQ, and the relative error in the convergence criteria for the MC and RQMC methods in order to get a comparable precision of the estimates. In a practical application this is unknown, but it is important to monitor this in order to make a fair comparison. That said, a particular advantage in practical applications of the MC method and the RQMC methods that we use is that, unlike GHQ, they provide an estimate of the error.

We performed 100 simulations for each combination of $n$ and $K$. We simulated the fixed offset, $X\beta$, and the covariance matrix of the random effects, $\Sigma$, in each of the 100 simulations to ensure that we test the methods on different data distributions. Details are provided in Appendix A. For all methods we required that the relative error of the log marginal likelihood estimate was expected to be around 0.0006 or less, such that we had three digits of precision.

Table 1 shows the median computation times. This gives an indication of the time it would take to approximate a marginal likelihood in seconds (obtained by multiplying the
Table 1: Median computation times in 1000th s of a second for a single cluster. $K$ is the number of random effect terms. For each combination $n$ and $K$, the fastest time is in bold. Some approximation methods failed to get an estimate within the required precision for some simulation samples. This was only the case for some of the non-adaptive version of the methods. Blank cells have not been run because of the long computation time.

| $n$ | Method/$K$ | 2   | 3   | 4   | 5   | 6   | 7   |
|-----|------------|-----|-----|-----|-----|-----|-----|
| 2   | GHQ        | 0.035 | 0.034 | 0.034 |
|     | AGHQ       | 0.033 | 0.030 | 0.030 | 0.033 | 0.032 | 0.030 |
|     | CDF        | **0.027** | **0.025** | **0.026** | **0.027** | **0.025** | **0.024** |
|     | Adaptive Genz & Monahan (1999) | 0.893 | 5.643 | 1.667 | 1.408 | 3.766 | 2.168 |
|     | RQMC       | 7.555 | 4.795 | 5.166 |
|     | Adaptive RQMC | 6.527 | 15.394 | 10.457 | 7.244 | 11.859 | 7.326 |
| 4   | GHQ        | 0.061 | 0.285 | 2.228 |
|     | AGHQ       | **0.043** | **0.161** | 0.991 | 0.863 | 0.807 | 0.816 |
|     | CDF        | 0.698 | 0.412 | **0.219** | **0.224** | **0.203** | **0.200** |
|     | Adaptive Genz & Monahan (1999) | 2.324 | 6.337 | 24.137 | 27.127 | 29.472 | 22.486 |
|     | RQMC       | 12.553 | 18.223 | 32.402 |
|     | Adaptive RQMC | 8.369 | 9.966 | 15.048 | 14.343 | 9.967 | 11.273 |
| 8   | GHQ        | 0.130 | 0.900 | 6.463 |
|     | AGHQ       | **0.061** | **0.268** | 1.667 | 5.942 | 52.379 | 217.768 |
|     | CDF        | 0.922 | 0.639 | **0.618** | **0.586** | **0.588** | **0.593** |
|     | Adaptive Genz & Monahan (1999) | 1.176 | 5.181 | 24.866 | 51.908 | 58.952 | 104.992 |
|     | RQMC       | 18.749 | 44.898 | 81.066 |
|     | Adaptive RQMC | 7.373 | 8.298 | 11.518 | 14.990 | 19.828 | 27.162 |
| 16  | GHQ        | 0.371 | 4.020 | 26.136 |
|     | AGHQ       | **0.094** | **0.336** | **1.736** | 10.452 | 62.796 | 341.623 |
|     | CDF        | 8.492 | 8.363 | 8.007 | **8.185** | **8.042** | **7.039** |
|     | Adaptive Genz & Monahan (1999) | 0.210 | 1.165 | 9.947 | 30.551 | 59.064 |
|     | RQMC       | 19.091 | 83.751 | 207.999 |
|     | Adaptive RQMC | 3.083 | 5.822 | 7.998 | 11.620 | 11.137 | 16.823 |
| 32  | AGHQ       | **0.151** | 0.609 | 3.264 | 19.634 | 118.587 | 629.202 |
|     | CDF        | 36.997 | 37.496 | 35.886 | 33.027 | 35.338 | 35.556 |
|     | Adaptive Genz & Monahan (1999) | 0.347 | 0.420 | **0.874** | **2.223** | **1.972** | 8.655 |
|     | RQMC       | 2.358 | 4.027 | 6.707 | 6.057 | 8.520 | **7.925** |

For both the GHQ and the GWI approximation implemented by Genz and Monahan (1999), it was preferable to use an adaptive procedure in all scenarios but we exclude the non-adaptive version of the latter because it was often extremely slow. The same conclusion applies for the RQMC method for the GWI but there is only a noticeable difference of a larger number of observations, $n$. The CDF approximation was clearly fastest for small clusters. However, the CDF approach was not preferable in all cases, as is argued or suggested by Barrett et al. (2015). For moderate cluster sizes, either the CDF or AGHQ approaches are...
Table 2: Median computation times in 1000th s of a second for a single cluster for the multinomial data. $K$ is the number of random effect terms and the number of categories. For each combination $n$ and $K$, the fastest time is in bold.

| $n$ | Method/$K$ | 3 | 4 | 5 | 6 |
|-----|------------|---|---|---|---|
| 2   | AGHQ       | 1.0 | 7.4 | 55.1 | 403 |
|     | CDF        | **0.4** | **0.4** | **0.6** | **3** |
|     | Adaptive Genz & Monahan (1999) | 0.6 | 113.5 | 119.8 | 381 |
|     | Adaptive RQMC | 21.1 | 72.4 | 70.2 | 124 |
| 4   | AGHQ       | 2.0 | 14.3 | 106.8 | 812 |
|     | CDF        | **0.6** | **4.8** | 7.6 | **16** |
|     | Adaptive Genz & Monahan (1999) | 1.2 | 28.6 | **3.0** | 146 |
|     | Adaptive RQMC | 22.2 | 56.3 | 46.0 | 88 |
| 8   | AGHQ       | 3.6 | 28.0 | 208.7 | 1545 |
|     | CDF        | 5.8 | 12.1 | 23.0 | 66 |
|     | Adaptive Genz & Monahan (1999) | **2.2** | **3.2** | **5.6** | **9** |
|     | Adaptive RQMC | 6.2 | 23.1 | 17.5 | 44 |
| 16  | AGHQ       | 4.8 | 27.6 | 169.2 | 1032 |
|     | CDF        | 13.5 | 35.0 | 80.7 | 186 |
|     | Adaptive Genz & Monahan (1999) | **4.4** | **6.6** | **11.2** | **17** |
|     | Adaptive RQMC | 11.2 | 19.6 | 30.4 | 43 |
| 32  | AGHQ       | **5.6** | 24.4 | 113.4 | 452 |
|     | CDF        | 42.8 | 120.9 | 264.6 | 642 |
|     | Adaptive Genz & Monahan (1999) | 8.8 | **12.8** | **22.5** | **29** |
|     | Adaptive RQMC | 21.4 | 37.6 | 59.6 | 72 |

fastest (depending on the number of random effect terms), and for large cluster sizes either AGHQ or an adaptive version of the GWI approximation suggested by Genz and Monahan (1999) or RQMC are to be preferred. The former is only attractive if $K$ is not too large as otherwise the $O((K^2 + nK)b^K)$ complexity starts to be an issue. The use of Equation (6) for $K > n$ with the GWIs is also clear in Table 1.

Next, we perform a similar simulation study with the mixed multinomial model presented in Section 4.2. We use one random effect per category, $K = c$, such that each category has a corresponding random effect which makes it more or less likely. We provide further details in Appendix A.1.

In this simulation, the CDF approach provides an approximation of a $n(c-1)$-dimensional integral whereas the GWI is $c = K$-dimensional. However, the integrand approximation we use for the GWI requires $8n(c-1)$ evaluations of the standard normal CDF (see Section A.1.1). In contrast, the CDF approximation only requires $nc$ evaluations. However, the GWI based approximations require only $K = c$ evaluations of the inverse standard normal CDF in contrast to the $n(c-1)$ evaluations used by the CDF approximation. The majority of the computation time with all our approximations is used on the standard normal CDF function or its inverse. Thus, this makes the CDF method seem attractive based purely on a per sample computational cost. However, the integral for the CDF approach quickly becomes rather high dimensional.

Table 2 shows the median computation times with multinomial data. The CDF approach is only the fastest option when $nc = nK$ is small compared to $K$. If this is not true, then AGHQ is best when $K = c$ is small and otherwise the MC method implemented by Genz
and Monahan (1999) is the fastest option. Lastly, it may be that the RQMC method would be the best alternative if a higher precision is required because of the RQMC method’s convergence rate.

The simulation examples we provide shows that there is not a single algorithm, among those that we consider, which is superior for all number of the random effect terms, $K$, and number of observations in a cluster, $n$, at a fixed precision of the estimate. In fact, in some cases there are substantial differences in the computation times of the different approximations.

6 Application to Salamander Mating

In this section, we fit a mixed binary model with crossed random effects to the salamander mating data described by McCullagh and Nelder (1989). Crossed random effects models are particularly difficult computationally as the log marginal likelihood typically ends up with terms of logs of moderate-to-high dimensional integrals. We will compare the CDF approximation, the MC approximation suggested by Genz and Monahan (1999), and the Laplace approximation. In our example, the first-order Laplace approximation is fast but yields downward biased estimates of the standard deviations of the random effects, as has been observed previously (Raudenbush et al., 2000; Pinheiro and Chao, 2006; Joe, 2008).

The binary outcome takes value one if the $i$th salamander mating pair is successful. Figure 2 in the appendix illustrates the design of the study. There are six clusters, each containing ten males and females which mates with each other in such a way that there are 60 attempted mating pairs in each cluster. Each salamander is either a whiteside or roughbutt breed. See McCullagh and Nelder (1989) for further details on the data set. We fit a model such that

$$U_k = (U_{kf}^T, U_{km}^T)^T \sim N^{(20)}(0, \text{diag}(\sigma_f^2 I, \sigma_m^2 I))$$

$$Y_{ki} \mid U = u \sim \text{Bin}(\Phi(\eta_{ki}), 1)$$

$$\eta_{ki} = \beta_0 + \beta_m I_m(k, i) + \beta_f I_f(k, i) + \beta_{mf} I_m(k, i) I_f(k, i) + u_{kff_i} + u_{kmf_i}$$

where $U_{km}$ and $U_{kf}$ are, respectively, male and female random effects in the $k$th cluster, $I_m(k, i)$ and $I_f(k, i)$ are indicators which take value one if, respectively, the male is the whiteside and the female is the whiteside, in the $i$th pair in the $k$th cluster, and $m_{ki}, f_{ki} \in \{1, \ldots, 10\}$ indicates which male and female is present in the $i$th pair in the $k$th cluster. See Pan and Thompson (2007) for a similar model using QMC but with a logit instead of probit link function.

The CDF version of the log marginal likelihood term for each cluster is the log of a 60-dimensional integral, while the GWI is 20-dimensional. Thus, we do not use AGHQ because of the $O\left((K^2 + nK)b^K\right)$ complexity. We fitted the model using a Laplace approximation using the lme4 package (Bates et al., 2015), using the CDF approximation, and using the approximation by Genz and Monahan (1998). The latter two include implemented approximations of the gradients. Both of our methods were first run with a high relative error in the convergence threshold with a maximum of 5000 samples for the GWI approximation.
and 10000 for the CDF approximation. We then used a lower convergence threshold with a maximum of 25000 samples and 50000 for the CDF.

The total estimation time using the CDF approximation was 20.5 seconds and the total estimation time of the method by [Genz and Monahan] (1998) was 20.2 seconds using 6 threads on a Laptop with an Intel® Core™ i7-8750H CPU, on Ubuntu 18.04 with our software compiled with gcc 8.3.0. The Laplace approximation was very fast and required only 0.3 seconds. Thus, we use the Laplace approximation to get starting values for the method which uses the CDF approximation and the method by [Genz and Monahan] (1998). We also used MCMC for a Bayesian version of the model with a normal distribution prior for each of the slopes with variance 10000 and a inverse gamma prior for each of the random effect variances with shape and rate parameter equal to 0.01. The MCMC estimation is performed in Stata ([StataCorp.] 2019) with 120000 samples where 20000 are used as burn-in. It took 770 seconds to draw the MCMC samples.

Table 3: Parameter estimates for the model for the salamander mating data. The MCMC row shows means of the posterior distribution. The row after the CDF and Genz et al. method are standard deviations of the estimates when different seeds are used (in parentheses). These are based on 50 different seeds.

|          | $\beta_0$ | $\beta_m$ | $\beta_f$ | $\beta_{mf}$ | $\sigma_f$ | $\sigma_m$ | Log-likelihood |
|----------|------------|------------|------------|--------------|------------|------------|----------------|
| CDF      | 0.612      | −0.425     | −1.707     | 2.110        | 0.700      | 0.670      | −206.877       |
|          | (0.006)    | (0.007)    | (0.009)    | (0.009)      | (0.006)    | (0.005)    |                |
| Genz et al. | 0.618      | −0.430     | −1.721     | 2.128        | 0.710      | 0.681      | −206.870       |
|          | (0.001)    | (0.002)    | (0.002)    | (0.003)      | (0.001)    | (0.001)    |                |
| Laplace  | 0.601      | −0.419     | −1.731     | 2.140        | 0.626      | 0.576      | −210.107       |
|          | (0.001)    | (0.002)    | (0.002)    | (0.003)      | (0.001)    | (0.001)    |                |
| MCMC means | 0.609      | −0.425     | −1.761     | 2.177        | 0.741      | 0.685      |                |

The estimated parameters are shown in Table 3. While the fixed effects, $\beta$, generally agree, the results suggest a large downward bias of the standard deviations with the Laplace approximation. The maximum likelihood estimates from the CDF and method by [Genz and Monahan] (1998) are very similar as expected. However, the CDF estimates are less precise in this case despite the comparable computation time.

7 Discussion

The methods described in this article, for fitting mixed effects models, are relevant in a variety of contexts, where practitioners may need guidance in choice of computational approach. In biostatistics, two uses of mixed models for which computational issues are important are accounting for sample relatedness in large genetic/biobank cohorts ([Zhou et al.] 2019) and family-based analysis of genetic and environmental contributions to complex survival and categorical outcomes ([Pawitan et al.] 2004; [Lichtenstein et al.] 2009). Other examples include crossed random effects such as the mixed model we estimate for the salamander data set.

We have shown that three different mixed effect models, mixed binomial models, mixed multinomial models, and mixed GSMs, all with a probit link function, have a similar log marginal likelihood where the log marginal likelihood terms, which are intractable, can be written as the log of a GWI and a multivariate normal CDF.
Our simulation example and application show that none of the approximation methods that we consider is best in all settings. This is in contrast with what other authors have argued. Particular methods can be biased or slow in certain settings. Our findings suggest that a hybrid procedure where different approximation methods are used for each intractable log marginal likelihood term may be optimal. Moreover, our simulations provide guidance concerning when to approximate the CDF and when to approximate the GWI and, if so, which method to use.

A considerable amount of computation time is spend on evaluating the standard normal CDF and its inverse with all methods we consider. In our experience, using a quicker but less precise method for the CDF may reduce the computation time for the methods we use with only a minor impact on the precision.

We have only applied the MC approximation of the CDF suggested by Genz (1992). Although the examples in Genz (1992) and Hajivassiliou et al. (1996) show that this method is extremely competitive, alternative approximation methods may be preferable for a low dimensional CDF. This is particularly true for the bivariate and trivariate normal distribution. Genz and Bretz (2009, Section 2.1 and 4.2) provide a number of alternatives. Thus, it might be possible to get a faster CDF approximation at a fixed precision by alternating between different CDF approximations. Furthermore, Botev (2017) has recently suggested to add minimax tilting to the method suggested by Genz (1992) and shown that the new approach is considerably better particularly in some higher dimensional scenarios. The new method may expand the settings in which the CDF approach is more attractive than approximating the GWI.

Despite that we have compared the CDF approach to a number of other approaches, our list of alternatives is not exhaustive. There are other approaches which can be used for approximating the marginal likelihood or for model estimation which are interesting. We provide a number of alternatives in Appendix B.

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A Simulation Study Details
Figure 2: Each column represents a female and each row represents a male. There is a square if a female and male have been mating.

For the simulation study in Section 5, the model we simulate from is

\[ \Sigma \sim W^{(K)} \left( \frac{1}{5K}, 5K \right) \]

\[ \eta_i = x_i^T \beta \sim N(0, 1) \]

\[ U \sim N^{(K)}(0, \Sigma) \]

\[ z_i = \left( K^{-1}, z_i^T \right)^T \]

\[ z_i' \sim N^{(K-1)} \left( 0, \frac{1}{K} I \right) \]

\[ y_i \sim \text{Bin}(\Phi(\eta_i + z_i^T u), 1) \]

for \( i = 1, \ldots, n \) where \( W^{(K)} \) denotes a \( K \)-dimensional Wishart distribution.

For each of the \( n \) and \( K \) pairs, we draw 100 samples from the above model. The goal is to use different methods to approximate the log marginal likelihood from taking the log after integrating out the complete data likelihood in Equation (16). First, we use the importance sampler described in Section 3.1.2. Let \( \hat{l}^{\text{IS}} \) and \( \hat{\sigma}^{\text{IS}} \) denote the estimate and MC standard error estimate, respectively, from the importance sampler. Then we start with \( 10 \cdot 10^6 \) samples and increase the number of samples to a maximum of \( 100 \cdot 10^6 \) until

\[ \hat{\sigma}^{\text{IS}} 4 < \hat{l}^{\text{IS}} 0.0002 \]

We fail to reach this precision in very few cases in which case we draw new parameters, random effects, and outcomes.

Next, we ensure the precision of MC methods. Let \( \hat{l}^{\text{CDF}}_i \) denote the log marginal likelihood estimate for \( i = 1, \ldots, 20 \) independent approximations with the CDF approach. For the CDF approach, we decrease the relative convergence threshold until \( \sqrt{20-1} \sum_{i=1}^{20} ((\hat{l}^{\text{CDF}}_i - \hat{l}^{\text{IS}})/\hat{l}^{\text{IS}})^2 < 0.0002 \). A similar procedure is used for the GWI approximation suggested by Genz and Monahan (1999) and the RQMC method. However, we use a maximum of 2500000 samples with all three methods.

Typically, it is suggested to increase the number of nodes when using quadrature and checking whether this effects the estimates. Thus, we use a number of nodes, \( b \), such that
using $b - 3, \ldots, b$ gives a similar scaled root mean square error as our MC or RQMC methods. We use a maximum of $b = 25$ nodes. All samples where any of the methods fail to reach the required precision are excluded. A few samples are excluded and those that are is because the non-adaptive methods fail to reach the required precision.

The cost of doing the above is not included in the computation times that we report. The computation times are computed by averaging over the computation times of 5 runs for each of the 100 samples given the relative error threshold or number of nodes. GHQ and AGHQ are implemented in C++. The GHQ rule is implemented with a slightly changed version of the C++ implementation in the fastGHQuad package (Blocker, 2018) which uses the method suggested by Golub and Welsch (1969). The time used to compute the rules is not included in the times that we report. Our RQMC method uses the Fortran code from the randtoolbox package (Christophe and Petr, 2020) which uses the code implemented by Bratley and Fox (1988) and Joe and Kuo (2003). This has allowed us to call the Fortran from C++ and avoid some large overhead which is present in the R interface of the randtoolbox in version 1.30.1. We use 10 scrambled Sobol sequences in our simulations.

The mode for the adaptive procedures is computed in C++ with the BFGS algorithm implemented in the C function vmmin used by R’s optim function with analytical gradients. The time used to find the mode is typically minor compared to the overall cost of the adaptive methods and is included in the reported computation times.

Table 4 shows the mean instead of median computation times in Table 1. The discrepancy between the median and mean shows that we need a lot of nodes or samples for some of the log marginal likelihoods that we approximate. Table 5 shows the average scaled root mean square error. This is computed as

$$\frac{1}{100} \sum_{i=1}^{100} \sqrt{\frac{5-1}{\hat{l}_{iS}^i}} \left( \frac{\hat{l}_{iCDF}^k - \hat{l}_{iS}^i}{\hat{l}_{iS}^i} \right)^2$$

for the CDF approximation where $\hat{l}_{iS}^i$ is the importance sampler estimate for the $i$th sample and $\hat{l}_{iCDF}^k$ is the $k$th run of the CDF approximation for the $i$th sample. A similar procedure is used for the MC methods for the GWI. The error for the GHQ and AGHQ is computed analogously using $b - 3, \ldots, b$ nodes. The latter implies that the MC based methods entries’ in Table 5 are not directly comparable with the deterministic GHQ and AGHQ method.

### A.1 Multinomial Model

For the multinomial model we cover in Section 4.2 we include a random effect term for each of the $c$ categories such that $K = c$. Each random effect term makes the corresponding category more or less likely within the cluster. In particular, the model we simulate from is

$$\Sigma \sim W(K) \left( \frac{1}{5K} I, 5K \right) \quad \eta_i = Bx_i \sim N(c)(0, I)$$

$$U \sim N(K)(0, \Sigma) \quad Z_i = I$$

$$A_i \mid U = u \sim N(Bx_i + Z_i u, I)$$
Table 4: Mean computation times in 1000th s of a second. K is the number of random effect terms. For each combination n and K, the fastest time is in bold. Some approximation methods failed to get an estimate within the required precision for some simulation samples. This was only the case for some of the non-adaptive version of the methods. Blank cells have not been run because of the long computation time.

| n  | Method/K | 2    | 3    | 4    | 5    | 6    | 7    |
|----|----------|------|------|------|------|------|------|
| 2  | GHQ      | 0.039| 0.038| 0.045|      |      |      |
|    | AGHQ     | 0.034| 0.031| 0.031| 0.034| 0.033| 0.031|
|    | CDF      | **0.026** | **0.027** | **0.027** | **0.026** | **0.025** |      |
|    | Adaptive Genz & Monahan (1999) | 39.740 | 32.548 | 23.679 | 18.927 | 20.653 | 19.373 |
|    | RQMC     | 7.963 | 5.268 | 5.752 |      |      |      |
|    | Adaptive RQMC | 56.247 | 68.340 | 49.651 | 25.804 | 38.465 | 32.497 |
| 4  | GHQ      | 0.065| 0.349| 2.669 |      |      |      |
|    | AGHQ     | **0.044** | **0.157** | 0.896 | 1.063 | 0.966 | 1.006|
|    | CDF      | 0.836 | 0.592 | **0.480** | **0.486** | **0.410** | **0.399** |
|    | Adaptive Genz & Monahan (1999) | 35.386 | 44.369 | 109.280 | 95.260 | 89.647 | 114.020 |
|    | RQMC     | 17.398 | 23.854 | 46.154 |      |      |      |
|    | Adaptive RQMC | 82.426 | 85.378 | 59.537 | 60.775 | 36.530 | 42.596 |
| 8  | GHQ      | 0.156 | 1.187 | 8.660 |      |      |      |
|    | AGHQ     | **0.064** | **0.256** | **1.475** | 9.065 | 61.779 | 398.004 |
|    | CDF      | 3.438 | 2.388 | 1.713 | **1.544** | **1.118** | **1.262** |
|    | Adaptive Genz & Monahan (1999) | 45.115 | 40.972 | 157.363 | 174.497 | 230.465 | 308.632 |
|    | RQMC     | 40.590 | 88.465 | 122.659 |      |      |      |
|    | Adaptive RQMC | 117.767 | 92.664 | 44.397 | 48.087 | 60.487 | 99.753 |
| 16 | GHQ      | 0.414 | 4.687 | 37.815 |      |      |      |
|    | AGHQ     | **0.095** | **0.398** | **2.167** | 14.551 | 91.090 | 519.403 |
|    | CDF      | 13.606 | 11.931 | 10.332 | **9.934** | **9.456** | **10.458** |
|    | Adaptive Genz & Monahan (1999) | 10.210 | 24.221 | 137.632 | 253.957 | 237.103 | 251.489 |
|    | RQMC     | 64.190 | 266.792 | 557.851 |      |      |      |
|    | Adaptive RQMC | 28.265 | 41.827 | 21.429 | 23.373 | 25.829 | 26.715 |
| 32 | AGHQ     | **0.153** | **0.635** | **3.181** | 21.026 | 112.693 | 634.481 |
|    | CDF      | 67.729 | 66.466 | 75.042 | **64.522** | **59.331** | **46.559** |
|    | Adaptive Genz & Monahan (1999) | 5.165 | 5.177 | 55.343 | 130.605 | 115.364 | 62.633 |
|    | RQMC     | 41.159 | 9.253 | 16.946 | **13.721** | **13.643** | **11.980** |

with

\[ Y_i = k \iff \forall k' \neq k' : A_{ik} > A_{ik'}, \quad k, k' \in \{1, \ldots, c\}. \]

The other settings are similar to those we use with the mixed binary model except that we use a required relative root mean square error of 0.0005 instead of 0.0002 to reduce the simulation time. The mean computation times are shown in Table 6 and average scaled root mean square errors are shown in Table 7.

### A.1.1 Multinomial Model’s Integrand

The GWI for the multinomial has an intractable integrand. That is, the conditional probability mass function in Equation (21) is intractable. We have implemented one-dimensional GHQ and AGHQ to approximate the integrand given the random effect, \( u \). In particular,
Table 5: Average scaled root mean square errors (in $10^{-5}$ s). $K$ is the number of random effect terms. Some approximation methods failed to get an estimate within the required precision for some simulation samples. This was only the case for some of the non-adaptive version of the methods. Blank cells have not been run because of the long computation time.

| $n$ | Method/K          | 2  | 3  | 4  | 5  | 6  | 7  |
|-----|-------------------|----|----|----|----|----|----|
| 2   | GHQ               | 4.35 | 5.15 | 4.99 |    |    |    |
|     | AGHQ              | 3.71 | 4.12 | 3.55 | 3.29 | 3.74 | 3.75 |
|     | CDF               | 0.63 | 0.92 | 0.70 | 0.56 | 0.66 | 0.65 |
|     | Adaptive Genz & Monahan (1999) | 6.90 | 6.77 | 6.64 | 6.98 | 6.60 | 7.54 |
|     | RQMC              | 7.57 | 7.62 | 7.03 |    |    |    |
|     | Adaptive RQMC     | 7.32 | 7.73 | 7.39 | 7.50 | 6.88 | 7.69 |
| 4   | GHQ               | 5.88 | 5.53 | 5.07 |    |    |    |
|     | AGHQ              | 3.56 | 3.60 | 3.52 | 3.42 | 3.56 | 3.55 |
|     | CDF               | 7.65 | 7.43 | 7.58 | 8.13 | 7.96 | 7.54 |
|     | Adaptive Genz & Monahan (1999) | 6.44 | 6.85 | 6.89 | 12.11 | 9.94 | 15.06 |
|     | RQMC              | 7.64 | 7.78 | 7.43 |    |    |    |
|     | Adaptive RQMC     | 8.21 | 8.11 | 7.02 | 7.55 | 7.43 | 7.62 |
| 8   | GHQ               | 6.15 | 5.86 | 5.26 |    |    |    |
|     | AGHQ              | 3.29 | 3.42 | 3.12 | 3.40 | 3.59 | 3.59 |
|     | CDF               | 7.67 | 7.78 | 7.84 | 8.38 | 7.69 | 7.10 |
|     | Adaptive Genz & Monahan (1999) | 6.24 | 6.49 | 8.30 | 8.14 | 8.56 | 13.89 |
|     | RQMC              | 7.38 | 7.81 | 8.08 |    |    |    |
|     | Adaptive RQMC     | 7.04 | 8.22 | 7.22 | 7.39 | 7.21 | 7.48 |
| 16  | GHQ               | 7.03 | 6.53 | 5.82 |    |    |    |
|     | AGHQ              | 3.96 | 3.29 | 3.31 | 3.58 | 3.05 | 3.75 |
|     | CDF               | 6.99 | 8.59 | 6.99 | 6.93 | 7.51 | 7.54 |
|     | Adaptive Genz & Monahan (1999) | 5.51 | 7.63 | 8.37 | 9.00 | 7.85 | 8.55 |
|     | RQMC              | 7.41 | 7.98 | 8.26 |    |    |    |
|     | Adaptive RQMC     | 7.26 | 7.54 | 7.80 | 7.21 | 7.62 | 7.25 |
| 32  | AGHQ              | 4.72 | 4.44 | 4.40 | 3.51 | 3.85 | 3.42 |
|     | CDF               | 7.41 | 7.18 | 7.44 | 7.78 | 8.30 | 7.43 |
|     | Adaptive Genz & Monahan (1999) | 5.27 | 6.39 | 7.93 | 8.02 | 8.10 | 8.99 |
|     | Adaptive RQMC     | 7.62 | 7.84 | 7.00 | 7.69 | 8.12 | 7.49 |

for given $\eta$ and $K$, we need an approximation of

$$h(u) = \int \phi(a)\Phi^{(c-1)}(1a + \eta + Ku) da,$$

$\partial/\partial u \log h(u)$, and $\partial^2/\partial u \partial u^\top \log h(u)$ where the latter two are needed for subsequent adaptive procedures. We perform a simulation study where we use the same setup as described in the previous section and evaluate the integrand above at the unknown random effect, $u$. Table 8 shows the average absolute relative error and Table 9 shows the average evaluation times. The adaptive version seems preferable. Thus, we have used the AGHQ version with 8 nodes given the errors shown in Table 8.

Moreover, the evaluation times in Table 9 shows that the integrand can be approximated in a few microseconds. While this is fast, it is an issue as we usually end with thousands of evaluations when we approximate the GWI.
Table 6: Mean computation times in 1000ths of a second for the multinomial data. $K$ is the number of random effect terms and the number of categories. For each combination $n$ and $K$, the fastest time is in bold.

| $n$ | Method/K | 3 | 4 | 5 | 6 |
|-----|----------|---|---|---|---|
| 2   | AGHQ     | 1.2 | 9 | 61 | 521 |
|     | CDF      | 0.6 | 1 | 2 | 3  |
|     | Adaptive Genz & Monahan (1999) | 19.0 | 345 | 499 | 947 |
|     | Adaptive RQMC | 44.2 | 134 | 98 | 181 |
| 4   | AGHQ     | 2.1 | 16 | 106 | 841 |
|     | CDF      | 1.8 | 5 | 10 | 17 |
|     | Adaptive Genz & Monahan (1999) | 30.9 | 368 | 143 | 864 |
|     | Adaptive RQMC | 78.8 | 115 | 66 | 122 |
| 8   | AGHQ     | 3.2 | 25 | 169 | 1165 |
|     | CDF      | 6.8 | 17 | 32 | 83 |
|     | Adaptive Genz & Monahan (1999) | 11.5 | 84 | 128 | 70 |
|     | Adaptive RQMC | 28.9 | 36 | 34 | 76 |
| 16  | AGHQ     | 4.4 | 25 | 167 | 1157 |
|     | CDF      | 17.8 | 49 | 112 | 263 |
|     | Adaptive Genz & Monahan (1999) | 4.5 | 7 | 11 | 18 |
|     | Adaptive RQMC | 12.6 | 22 | 33 | 45 |
| 32  | AGHQ     | 5.9 | 25 | 116 | 478 |
|     | CDF      | 47.4 | 229 | 403 | 1006 |
|     | Adaptive Genz & Monahan (1999) | 8.9 | 13 | 23 | 30 |
|     | Adaptive RQMC | 23.2 | 38 | 61 | 72 |

B Alternative Approximations

We describe alternative approximations in this section which we have not implemented but which have, for particular models, received attention by other authors, which we find to be promising but overlooked, or which may be useful for practitioners in particular cases.

B.1 Variational Approximations

We will discuss applications of variational approximations (VAs) in this section. We will only give a brief introduction to VAs. See Bishop (2006) and Ormerod and Wand (2010) for an introduction to VAs and examples of VAs. A typical VA uses some family of variational distributions denoted by $q$ parameterized by some set $\Theta$, which is used in the lower bound of the log marginal likelihood. This can be derived by writing the log marginal likelihood as

\[
l(\beta, \Sigma) = \int q(\bm{u}; \Theta) \log \left( \frac{p(\bm{y}, \bm{u})}{q(\bm{u}; \Theta)} \frac{p(\bm{u} | \bm{y})}{q(\bm{u}; \Theta)} \right) d\bm{u}
\]

\[
= \int q(\bm{u}; \Theta) \log \left( \frac{p(\bm{y}, \bm{u})}{q(\bm{u}; \Theta)} \right) d\bm{u} + \int q(\bm{u}; \Theta) \log \left( \frac{q(\bm{u}; \Theta)}{p(\bm{u} | \bm{y})} \right) d\bm{u}
\]

Thus

\[
l(\beta, \Sigma) \geq \int q(\bm{u}; \Theta) \log \left( \frac{p(\bm{y}, \bm{u})}{q(\bm{u}; \Theta)} \right) d\bm{u} = \tilde{l}(\beta, \Sigma, \Theta)
\]
Table 7: Average scaled root mean square errors (in $10^{-5}$s) for the multinomial data. $K$ is the number of random effect terms and the number of categories.

| $n$ | Method/K       | 3  | 4  | 5  | 6  |
|-----|----------------|----|----|----|----|
| 2   | AGHQ           | 6.84 | 8.92 | 8.41 | 8.57 |
|     | CDF            | 19.45 | 19.51 | 21.59 | 20.84 |
|     | Adaptive Genz & Monahan (1999) | 17.06 | 19.85 | 18.37 | 21.65 |
|     | Adaptive RQMC  | 20.98 | 18.21 | 19.87 | 19.21 |
| 4   | AGHQ           | 7.02 | 8.00 | 5.81 | 6.60 |
|     | CDF            | 20.65 | 21.94 | 19.40 | 17.81 |
|     | Adaptive Genz & Monahan (1999) | 13.97 | 19.32 | 18.75 | 18.69 |
|     | Adaptive RQMC  | 19.08 | 19.28 | 19.24 | 19.95 |
| 8   | AGHQ           | 7.99 | 7.91 | 7.19 | 7.65 |
|     | CDF            | 20.73 | 20.90 | 19.91 | 20.79 |
|     | Adaptive Genz & Monahan (1999) | 7.21 | 14.54 | 12.26 | 17.67 |
|     | Adaptive RQMC  | 18.28 | 20.67 | 19.58 | 20.24 |
| 16  | AGHQ           | 13.19 | 12.50 | 11.73 | 11.04 |
|     | CDF            | 20.71 | 18.74 | 19.18 | 18.82 |
|     | Adaptive Genz & Monahan (1999) | 3.16 | 5.25 | 6.28 | 8.85 |
|     | Adaptive RQMC  | 12.37 | 14.16 | 12.68 | 15.35 |
| 32  | AGHQ           | 8.53 | 9.39 | 11.98 | 13.17 |
|     | CDF            | 19.12 | 17.59 | 18.75 | 17.05 |
|     | Adaptive Genz & Monahan (1999) | 1.61 | 2.36 | 1.76 | 2.58 |
|     | Adaptive RQMC  | 5.23 | 5.88 | 5.88 | 5.61 |

for each $\theta \in \Theta$. The right hand side of the inequality is a lower bound since the Kullback–Leibler (KL) divergence

$$\int q(u; \theta) \log \left( \frac{q(u; \theta)}{p(u | y)} \right) du$$

is positive. The idea is to maximize the lower bound, $\tilde{l}(\beta, \Sigma, \theta)$, with respect to $\theta$ to get a tighter lower bound of the log marginal likelihood. This is equivalent to minimizing the KL divergence between $q$ and the conditional density of the random effect, $U$, given the observed data, $y$. In particular, if $q(u; \theta) = p(u | y)$ then the lower bound is equal to the log marginal likelihood. The final VA is then given by

$$\arg \max_{\beta, \Sigma, \theta} \tilde{l}(\beta, \Sigma, \theta)$$

The important part of a VA is to choose a family of variational distributions such that it is easy to optimize the lower bound and which yields a tight lower bound or at least a lower bound that has a similar shape as the log marginal likelihood as a function of the model parameters, $\beta$ and $\Sigma$. The latter implies that one needs a family of variational distributions which has some $\theta \in \Theta$ such that the KL divergence between the conditional density of the random effects, $U$, given the observed data, $y$, is small.

Two related VAs are shown for the mixed binomial model shown in Section 4.1 by Consonni and Marin (2007) and the mixed multinomial model in Section 4.2 by Girolami and Rogers (2006). However, the example in Consonni and Marin (2007) shows that such a VA
Table 8: Mean absolute relative error times $10^3$ from 100 simulations for the integrand in the multinomial model in the GWI. The first column shows the number of quadrature nodes.

| K     | Method/n | 2   | 4   | 8   | 2   | 4   | 8   | 2   | 4   | 8   |
|-------|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 4     | AGHQ     | 0.216 | 0.280 | 0.308 | 0.215 | 0.291 | 0.299 | 0.292 | 0.304 | 0.319 |
|       | GHQ      | 25.521 | 109.780 | 215.267 | 112.981 | 249.999 | 87.333 | 167.709 | 441.312 |
| 8     | AGHQ     | 0.002 | 0.005 | 0.013 | 0.004 | 0.011 | 0.023 | 0.007 | 0.016 | 0.028 |
|       | GHQ      | 0.517 | 7.053 | 25.589 | 1.312 | 6.463 | 30.082 | 3.613 | 14.542 | 62.799 |
| 16    | AGHQ     | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
|       | GHQ      | 0.001 | 0.079 | 0.261 | 0.005 | 0.121 | 0.658 | 0.030 | 0.225 | 2.447 |
| 32    | AGHQ     | 0.000 | 0.000 | 0.001 | 0.000 | 0.000 | 0.002 | 0.000 | 0.000 | 0.009 |
|       | GHQ      | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

Table 9: Average evaluation times in microseconds from 100 simulations for the integrand in the multinomial model in the GWI. The first column shows the number of quadrature nodes.

| K     | Method/n | 2   | 4   | 8   | 2   | 4   | 8   | 2   | 4   | 8   |
|-------|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 4     | AGHQ     | 0.91 | 1.48 | 2.76 | 1.51 | 2.79 | 5.43 | 2.11 | 4.30 | 8.55 |
|       | GHQ      | 0.62 | 0.99 | 1.81 | 1.05 | 1.87 | 3.57 | 1.46 | 2.84 | 5.35 |
| 8     | AGHQ     | 1.53 | 2.52 | 4.82 | 2.61 | 4.89 | 9.70 | 3.74 | 7.68 | 15.26 |
|       | GHQ      | 1.24 | 2.00 | 3.65 | 2.06 | 3.78 | 7.21 | 2.91 | 5.74 | 10.93 |
| 16    | AGHQ     | 2.81 | 4.67 | 8.92 | 4.82 | 9.00 | 17.94 | 6.86 | 14.38 | 28.45 |
|       | GHQ      | 2.48 | 4.05 | 7.46 | 4.16 | 7.57 | 14.58 | 5.88 | 11.80 | 22.22 |
| 32    | AGHQ     | 5.40 | 8.97 | 17.08 | 9.10 | 17.12 | 34.09 | 13.08 | 27.38 | 54.02 |
|       | GHQ      | 4.94 | 8.20 | 15.19 | 8.36 | 15.34 | 34.09 | 13.08 | 27.38 | 54.02 |

may work poorly in certain settings. We now discuss an alternative VA and provide good arguments for why this VA may work well.

We know that the conditional density of the random effects given the observed data is in the form of the density of a generalized skew-normal distribution which density is shown in Equation (11). This reduces to the multivariate skew-normal distribution

$$q(v_1; \xi_1, \Xi_{11}, \alpha) = 2\phi^{(k_1)}(v_1; \xi_1, \Xi_{11})\Phi\left((\alpha \cdot \text{diag}(\Xi_{11})^{-1/2})^\top(v_1 - \xi_1)\right)$$

when $k_2 = 1$, $v_2 = 0$, $\xi_2 = 0$, $-\Xi_{21}\Xi_{11}^{-1} = (\alpha \cdot \text{diag}(\Xi_{11})^{-1/2})$, and $\Xi_{22} - \Xi_{21}\Xi_{11}^{-1}\Xi_{12} = 1$. This is interesting as this suggest that the skew-normal VA shown by Ormerod (2011) may work well for these models. This is nice since Ormerod (2011) shows that a skew-normal VA still yields a quite tractable and otherwise easy to approximate lower bound in models like or similar to those that we discuss in this paper. Moreover, some of our separate work suggest that a skew-normal VA works well for mixed GSMs in the sense of providing a very tight lower bound and by being fast to optimize.

If a skew-normal VA as suggested in Ormerod (2011) does not yield a tight lower bound, two possible generalization of the skew-normal VA are

$$q(v_1; \xi_1, \Xi_{11}, \Lambda) = 2^k\phi^{(k_1)}(v_1; \xi_1, \Xi_{11})\Phi^{(k)}(\Lambda(v_1 - \xi_1))$$

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or
\[ q(v_1; \xi_1, \Xi_{11}, \lambda, \Lambda, \Xi_{22}) = \phi^{(k_1)}(v_1; \xi_1, \Xi_{11}) \frac{\phi^{(k)}(\Lambda^{-1/2}(v_1 - \xi_1))}{\phi^{(k)}(\lambda; 0, I + \Lambda^{-1} \Lambda^\top)} \]

with \(1 \leq k < k_2\), \(\Lambda \in \mathbb{R}^{k \times k_1}\), and \(\lambda \in \mathbb{R}^k\).

Using an unconstrained skew-normal VA such as suggested by Ormerod (2011) requires estimation of \(O(K^2)\)-parameters. The question then is at what rate one can estimate these parameters. A constrained variational distribution can be used such that there are only say \(O(K)\)-parameters (e.g. by using a diagonal scale matrix). Of course, this will result in a less tight lower bound.

To summarize, there are good arguments for using a skew-normal VA or generalization of it for the class of models that we consider in this paper. Despite these arguments, such approximations have received limited attention. This is a promising avenue of research for the future, which we are currently pursuing, but is beyond the scope of this paper.

B.2 Expectation Maximization

A common type of method to estimate mixed models is to use an expectation maximization (EM) algorithm (Dempster et al., 1977). However, the E-step of the EM algorithm cannot be solved analytically in general for the class of models which we consider. Thus, some type of quadrature, alternative deterministic procedure, or MC method is needed. Further, the M-step is typically much easier to compute if an expectation conditional maximization (ECM) algorithm is used (Meng and Rubin, 1993).

Some authors have suggested MC versions of an ECM algorithm. Two examples are Hughes (1999); Vaida et al. (2007) who develop such algorithms which are easily changed to be applicable for the mixed GSM model we consider in Section 4.3. Two disadvantages of such an algorithm are the sometimes slow convergence of EM algorithms, and that the guarantee that the likelihood is increasing in every iteration is lost because of MC approximation in the E-step.

B.3 Hybrid Laplace Approximation

We have already shown the Laplace approximation in Section 3.1.1 and provided an application where the estimated standard deviations of the random effects are downward biased. Interestingly, a hybrid MC and Laplace approximation can be considered. In particular, the method suggested by Lai and Shih (2003) can be used for the mixed binomial model in Section 4.1. With this method, a metric is computed to judge whether or not a Laplace approximation is going to give a precise estimate of the log marginal likelihood term for a given cluster. A MC method is used if this is not the case.

Using such a hybrid method in combination with either a MC estimator of the GWI, AGHQ, or the CDF approximation depending on the size of the random effects, dimension of the CDF approximation, and the mean and covariance matrix can potentially result in a fast and precise method for a large group of data sets and class of models. That is, it might be possible to develop a heuristic for when to use which approximation which is applicable
to all the mixed models that we discuss in this paper. However, it is beyond the scope of this paper to develop and implement such a hybrid method.

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