

Generalized Linear Mixed Models in Dairy Cattle Breeding¹

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ABSTRACT

Fitness and fertility traits of dairy cattle are of increasing importance and are often measured on a discrete scale. The development and application of generalized linear mixed models to the genetic analysis of these traits are reviewed. Because current genetic evaluation systems are predominantly based on animal models, the inferential challenges of highly parameterized generalized linear mixed models are discussed. Development and adoption of new methods for drawing appropriate inferences on dispersion parameters are essential. Recent hierarchical extensions have been proposed for generalized linear mixed models, allowing for complex dispersion patterns that accommodate heteroscedasticity and outlier robustness. Steady advances in available computing power have facilitated multiple-trait analyses involving continuous and discrete measures. Full Bayesian inference via the development of Markov Chain Monte Carlo methods will continue to allow even greater generality and dimensions in the genetic model.

(**Key words:** generalized linear mixed models, Laplacian estimation, Gibbs sampling, animal models)

Abbreviation key: **ECP** = extreme category problem, **EM** = expectation-maximization, **FCD** = full conditional density, **GLMM** = generalized linear mixed model, **MAP** = maximum a posteriori, **MCMC** = Markov Chain Monte Carlo, **ML** = maximum likelihood, **MML** = marginal maximum likelihood.

INTRODUCTION

Selection objectives for dairy cattle in North America have historically emphasized milk production. However, other traits, often referred to as secondary or nonproduction traits, are also important for economic efficiency. In North America, secondary traits of interest predominantly have been measures

of conformation. However, many conformation traits are not directly related to lifetime profitability or herd life, and some relationships are plausibly distorted (e.g., because of differences in selection practices between registered and grade herds) (18). Health and reproductive fitness, however, directly affect dairy production profitability. A recent survey of the Michigan dairy industry targeted cow reproduction and health as the highest priority issue after business and financial management. Fertility problems account for 16 to 28% of all involuntary disposals (40) and limit efficiency of present AI progeny-testing schemes. Issues of udder health are also important and include IMI, clinical mastitis, and food safety issues involving drug residues.

Shook (74) considered genetic variation for disease traits to be substantial enough to warrant consideration in breeding programs. Outside of involuntary culling, however, selection pressure for fitness and fertility of dairy cattle has been virtually nonexistent in North America for several reasons. Current recording systems are primarily focused on the collection of production and conformation data. Also, statistical genetic modeling of these traits is perceived to be somewhat formidable relative to the genetic evaluation of normally distributed traits. This apparent difficulty is related to the fact that these traits are generally measured on a discrete scale such that a structural relationship exists between the mean and variance of each observation. Therefore, statistical genetic analyses based on linear mixed models are generally unsuitable for such traits, even if attempts are made to account for the heteroscedasticity (60). Somatic cell counts of milk samples are currently used to assess udder health indirectly, and genetic evaluations are available (73). The basis for the use of SCC is its relative ease of supervised recording, its moderate genetic correlation with IMI or clinical mastitis, and its higher heritability. However, to the author's knowledge, all such studies used to estimate this genetic correlation have not appropriately allowed for the discrete nature of data on clinical mastitis or IMI in a multiple-trait analysis with SCC.

Generalized linear models (57) and their extended mixed effects versions (4) account for the distribu-

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tional nature of discrete data in the modeling of expected responses as a function of risk factors. These models have been increasingly used for binary data (45) and counted data (51, 72, 94) from epidemiology and reproductive physiology research. Furthermore, sire model versions of generalized linear mixed models (**GLMM**) have been used in dairy breeding research (8, 9, 68, 76, 87, 93). This emphasis on the sire model continues today despite the increasing use of animal models for the genetic evaluation of continuous production traits. This paper briefly reviews the theory and applications of GLMM in animal breeding research. Alternative methods for the estimation of genetic parameters are discussed, and some of their properties are demonstrated by simulation. Also, emphasis is placed on GLMM that are flexible enough to capture the most salient features of biological processes and management conditions. In line with most animal breeding GLMM research thus far, Bayesian approaches to statistical genetic inference are emphasized.

METHODOLOGICAL DEVELOPMENT

The simplest case of a GLMM is the linear mixed model, but, throughout this review, the term GLMM is reserved for data situations other than normally distributed traits. The linear mixed model is written

$$\mathbf{y} = \eta + \mathbf{e} = \mathbf{X}\beta + \mathbf{Z}\mathbf{u} + \mathbf{e} \tag{1}$$

where $\mathbf{y} = \{y_i\} = n \times 1$ vector of observations, $\beta = p \times 1$ vector of fixed effects, and $\mathbf{u} = q \times 1$ vector of random effects defined such that, a priori,

$$\mathbf{u} | \sigma_u^2 \sim \pi(\mathbf{u} | \sigma_u^2) = N(\mathbf{0}, \mathbf{G}) \tag{2}$$

where \mathbf{X} and \mathbf{Z} = design matrices that link the elements of β and \mathbf{u} , respectively, to elements of \mathbf{y} or its conditional expectation $\eta = \{\eta_i\} = E(\mathbf{y} | \beta, \mathbf{u})$. Also, $\mathbf{e} \sim N(\mathbf{0}, \mathbf{R})$ = vector of normally distributed residuals for which, typically, $\mathbf{R} = \mathbf{I}\sigma_e^2$ in univariate animal breeding analyses. This relationship is equivalent to specifying the sampling density or likelihood of the data as normal or Gaussian:

$$\mathbf{y} | \beta, \mathbf{u}, \sigma_e^2 \sim \pi(\mathbf{y} | \beta, \mathbf{u}, \sigma_e^2) = N(\mathbf{X}\beta + \mathbf{Z}\mathbf{u}, \mathbf{R}). \tag{3}$$

For pedagogical reasons, in this paper, we often consider the case of one random factor where \mathbf{u} is typically the vector of additive genetic or sire effects with $\mathbf{G} = \mathbf{A}\sigma_u^2$. \mathbf{A} is then a known matrix of additive

genetic relationships, and σ_u^2 is the additive genetic variance. If several, say c , random factors exist, then $\mathbf{u}' = [\mathbf{u}'_1 \ \mathbf{u}'_2 \ \dots \ \mathbf{u}'_c]$ with $\mathbf{G} = \text{var}(\mathbf{u})$ being a function of several (co)variance components in a vector σ and several known correlation (relationship) matrices.

In one derivation of BLUP, Henderson et al. (33) maximized the joint density of \mathbf{y} and \mathbf{u} or the product of [3] and [2]:

$$\pi(\mathbf{y}, \mathbf{u} | \beta, \sigma_e^2, \sigma_u^2) = \pi(\mathbf{y} | \beta, \mathbf{u}, \sigma_e^2) \pi(\mathbf{u} | \sigma_u^2) \tag{4}$$

with respect to β and \mathbf{u} , conditional on known variances or ratios thereof. Using first derivatives, this maximization led to the mixed model equations (33):

$$\begin{bmatrix} \mathbf{X}'\mathbf{R}^{-1}\mathbf{X} & \mathbf{X}'\mathbf{R}^{-1}\mathbf{Z} \\ \mathbf{Z}'\mathbf{R}^{-1}\mathbf{X} & \mathbf{Z}'\mathbf{R}^{-1}\mathbf{Z} + \mathbf{G}^{-1} \end{bmatrix} \begin{bmatrix} \hat{\beta} \\ \hat{\mathbf{u}} \end{bmatrix} = \begin{bmatrix} \mathbf{X}'\mathbf{R}^{-1}\mathbf{y} \\ \mathbf{Z}'\mathbf{R}^{-1}\mathbf{y} \end{bmatrix} \tag{5}$$

Henderson (31) showed that $\hat{\beta}$ = BLUE of β , and $\hat{\mathbf{u}}$ = BLUP of \mathbf{u} . As noted by Lindley and Smith (52) and, in an animal breeding context, by Gianola and Fernando (22), this combination of data likelihood $\pi(\mathbf{y} | \beta, \mathbf{u}, \sigma_e^2)$ with prior $\pi(\mathbf{u} | \sigma_u^2)$ also defines a two-stage hierarchical Bayes model with two assumptions: 1) the fixed and random effects are a priori independent with $\pi(\beta, \mathbf{u} | \sigma_u^2) \propto \pi(\beta) \pi(\mathbf{u} | \sigma_u^2)$, and 2) a flat prior $\pi(\beta) \propto 1$ is specified as typifies a Bayesian fixed effect. Hence, $\pi(\beta, \mathbf{u} | \sigma_u^2) \propto \pi(\mathbf{u} | \sigma_u^2)$ such that the joint posterior density of the location parameters can be written similarly to [4]:

$$\pi(\beta, \mathbf{u} | \sigma_e^2, \sigma_u^2, \mathbf{y}) \propto \pi(\mathbf{y} | \beta, \mathbf{u}, \sigma_e^2) \pi(\mathbf{u} | \sigma_u^2) \pi(\beta); \tag{6}$$

that is, $\pi(\beta, \mathbf{u} | \sigma_e^2, \sigma_u^2, \mathbf{y}) \propto \pi(\mathbf{y}, \mathbf{u} | \beta, \sigma_e^2, \sigma_u^2)$ when $\pi(\beta) \propto 1$. Therefore, $\hat{\beta}$ and $\hat{\mathbf{u}}$ are also the joint posterior modal estimates of β and \mathbf{u} , respectively.

As already indicated, the Gaussian sampling density in Equation [3] is not appropriate for discrete data, thereby making BLUP a generally unsuitable method for computing genetic evaluations on fitness and fertility traits. However, any probability distribution in the exponential family can be used to characterize the sampling distribution of the data in a classical generalized linear model; examples include the binomial distribution for binary data, the multinomial distribution for ordinal categorical data, and the Poisson distribution for count data (57). Let \mathbf{x}'_i denote row i of \mathbf{X} and \mathbf{z}'_i denote row i of \mathbf{Z} . Then, the

expectation of each observation y_i can be written as a function of the fixed and random effects:

$$E(y_i | \eta_i) = h(\eta_i). \quad [7]$$

where $\eta_i = \mathbf{x}'_i \boldsymbol{\beta} + \mathbf{z}'_i \mathbf{u}$. For example, $h(\cdot)$ is simply the identity function in the linear mixed model [1] such that $E(y_i | \eta_i) = \eta_i$. In most cases, $h(\cdot)$ is defined such that $-\infty < \eta_i = h^{-1}(E(y_i)) < \infty$; h^{-1} is referred to as the link function. This link allows any estimates of $\boldsymbol{\beta}$ and \mathbf{u} on real space while restricting the estimated means $\hat{E}(y_i) = h(\hat{\eta}_i)$ to fall within the allowable parameter space. The first mixed effects version of generalized linear models for the genetic analysis of discrete data in animal breeding was independently developed by Gianola and Foulley (23) and Harville and Mee (30), who were particularly concerned about the quantitative genetic analysis of calving ease, an ordinal scored categorical trait for which dairy sire genetic evaluations are currently provided (3). Consider the binomial or, more specifically, the Bernoulli distribution for modeling binary data on an observation by observation basis, as in an animal model with no repeated records. Let p_i denote the probability of success for cow i , the success event being, for example, a case of clinical mastitis. Then, the Bernoulli distribution for the incidence of clinical mastitis in cow i , with $y = 0$ denoting the healthy condition and $y = 1$ denoting the diseased condition, is

$$\text{Prob}(Y_i = y | p_i) = (p_i)^y (1 - p_i)^{1-y}. \quad [8]$$

The link function of choice for modeling ordered categorical data in animal breeding is generally the probit function Φ^{-1} . That is, using [7], $E(y_i | p_i) = p_i = \Phi(\mathbf{x}'_i \boldsymbol{\beta} + \mathbf{z}'_i \mathbf{u})$ where Φ is simply the cumulative distribution function for the standard normal distribution. The biological appeal of the probit link arises from the equivalency of this model to one that conceptualizes an underlying liability variate l_i for cow i . Here, l_i is a linear function of an unstandardized version of η_i and a normal residual e_i . If l_i lies to the right of a threshold point, say τ , then cow i is diseased or $y_i = 1$; otherwise, the cow is healthy, or $y_i = 0$ (23). Note that the probit link appropriately constrains the probability parameter for cow i to $0 \leq p_i \leq 1$, but the identity link of the linear mixed model does not. The contribution of the observation y_i to the data likelihood function for $\boldsymbol{\beta}$ and \mathbf{u} given [8] can then be written as

$$l_i(\boldsymbol{\beta}, \mathbf{u} | y_i) \propto \left(\Phi(\mathbf{x}'_i \boldsymbol{\beta} + \mathbf{z}'_i \mathbf{u}) \right)^{y_i} \left(1 - \Phi(\mathbf{x}'_i \boldsymbol{\beta} + \mathbf{z}'_i \mathbf{u}) \right)^{1-y_i}. \quad [9]$$

Here $l_i(\boldsymbol{\beta}, \mathbf{u} | y_i) \equiv \pi(y_i | \boldsymbol{\beta}, \mathbf{u})$, and the likelihood notation $l_i(\cdot | \cdot)$ reflects its emphasis as a function of the parameters. Suppose n such individuals with records y_1, y_2, \dots, y_n in \mathbf{y} are observed. The likelihood function given all data is then a product of the individual likelihood contributions, assuming that the observations are conditionally (on $\boldsymbol{\beta}$ and \mathbf{u}) independent of each other:

$$l(\boldsymbol{\beta}, \mathbf{u} | \mathbf{y}) \equiv \pi(\mathbf{y} | \boldsymbol{\beta}, \mathbf{u}) \propto \prod_{i=1}^n l_i(\boldsymbol{\beta}, \mathbf{u} | \sigma_u^2, y_i) = \prod_{i=1}^n \left(\Phi(\mathbf{x}'_i \boldsymbol{\beta} + \mathbf{z}'_i \mathbf{u}) \right)^{y_i} \left(1 - \Phi(\mathbf{x}'_i \boldsymbol{\beta} + \mathbf{z}'_i \mathbf{u}) \right)^{1-y_i}. \quad [10]$$

Note that there is no scale or extra dispersion parameter specified in $\pi(\mathbf{y} | \boldsymbol{\beta}, \mathbf{u})$ analogous to σ_e^2 in a Gaussian sampling density; the sampling mean and variance for y_i are determined solely by p_i , which may not necessarily be a desirable feature for some GLMM, as is discussed later.

As with the Bayesian mixed effects model of Gianola and Fernando (22), a flat prior $\pi(\boldsymbol{\beta}) \propto 1$ on the fixed effects and an informative prior $\mathbf{u} | \sigma_u^2 \sim \pi(\mathbf{u} | \sigma_u^2) = N(\mathbf{0}, \mathbf{G})$ on the random effects are specified. Then, the joint posterior density of the fixed and random effects, conditional on σ_u^2 , is written to be similar to [6], except that the sampling distribution is binary rather than Gaussian:

$$\pi(\boldsymbol{\beta}, \mathbf{u} | \sigma_u^2, \mathbf{y}) \propto \pi(\mathbf{y} | \boldsymbol{\beta}, \mathbf{u}) \pi(\mathbf{u} | \sigma_u^2) \pi(\boldsymbol{\beta}) \propto \prod_{i=1}^n \left(\left(\Phi(\mathbf{x}'_i \boldsymbol{\beta} + \mathbf{z}'_i \mathbf{u}) \right)^{y_i} \left(1 - \Phi(\mathbf{x}'_i \boldsymbol{\beta} + \mathbf{z}'_i \mathbf{u}) \right)^{1-y_i} \right) \exp \left(-\frac{\mathbf{u}' \mathbf{A}^{-1} \mathbf{u}}{2\sigma_u^2} \right). \quad [11]$$

This joint density defines the threshold mixed model for the quantitative genetic analysis of binary data in animal breeding; extensions to more than two ordinal categories of response have been developed by Gianola and Foulley (23) and Harville and Mee (30). Those scientists developed a scoring method set of equations to maximize this joint posterior density with respect to $\boldsymbol{\beta}$ and \mathbf{u} . Those equations closely resemble Henderson's mixed model equations in [5].

Representing $\boldsymbol{\theta} = \begin{bmatrix} \boldsymbol{\beta} \\ \mathbf{u} \end{bmatrix}$ as the vector of location parameters, the coefficient matrix for the Newton-Raphson iterative set of equations can be written as

$$\mathbf{H}_\sigma = - \frac{\partial^2 \log \pi(\theta | \sigma_u^2, \mathbf{y})}{\partial \theta \partial \theta'}, \tag{12}$$

which for the threshold mixed model in [11] is

$$\begin{bmatrix} \mathbf{X}'\mathbf{R}\mathbf{X} & \mathbf{X}'\mathbf{R}\mathbf{Z} \\ \mathbf{Z}'\mathbf{R}\mathbf{X} & \mathbf{Z}'\mathbf{R}\mathbf{Z} + \mathbf{G}^{-1} \end{bmatrix} \tag{13}$$

where \mathbf{R} is now a diagonal $n \times n$ matrix with diagonal element i being

$$r_{ii} = \left(\frac{\phi(\eta_i)}{1 - \Phi(\eta_i)} \right)^2 - \frac{\phi(\eta_i)\eta_i}{1 - \Phi(\eta_i)} \tag{14a}$$

if $y_i = 0$ and

$$r_{ii} = \left(\frac{\phi(\eta_i)}{\Phi(\eta_i)} \right)^2 - \frac{\phi(\eta_i)\eta_i}{\Phi(\eta_i)} \tag{14b}$$

if $y_i = 1$. Here, ϕ denotes the standard normal density function. Note that the coefficient matrix in [13], with elements defined in [14a] and [14b], differs from that for the Fisher scoring implementation of Gianola and Foulley (23). The coefficient matrix in Fisher scoring is $E_y(\mathbf{H}_\sigma)$ or the expected value of \mathbf{H}_σ over \mathbf{y} .

The modal estimates $\hat{\theta}_\sigma = \text{Arg}_\theta \text{Max} \pi(\theta | \sigma_u^2, \mathbf{y})$ of the fixed and random effects are identical under Newton-Raphson and Fisher scoring implementations and are typically termed the maximum a posteriori (MAP) estimates (15). Further approximate inference (i.e., standard errors of prediction) is generally based on $\hat{\text{v}}\hat{\text{a}}\hat{\text{r}}(\theta | \sigma_u^2, \mathbf{y}) \approx \hat{\mathbf{H}}_\sigma^{-1}$ or $\hat{\text{v}}\hat{\text{a}}\hat{\text{r}}(\theta | \sigma_u^2, \mathbf{y}) \approx E_y(\hat{\mathbf{H}}_\sigma^{-1})$ where $\hat{\mathbf{H}}_\sigma^{-1} = \mathbf{H}_\sigma^{-1}$ evaluated at $\hat{\theta}_\sigma$. These computations are very much analogous to linear mixed model implementations. Therefore, implementations of GLMM should not be considered to be appreciably difficult relative to computation of estimated breeding values using a linear mixed model.

GENETIC PARAMETER ESTIMATION

Perhaps the most contentious issue in the implementation of GLMM for the analysis of discrete data has been the estimation of variance components. That is, in most cases, σ_u^2 is not known and must be estimated. Therefore, a third-stage prior on σ_u^2 is needed, thereby defining a three-stage hierarchical Bayes model. Furthermore, an optional scale parameter α might be specified to allow for any over-

dispersion (83) beyond that specified in a one-parameter (i.e., η_i) sampling distribution. For the purposes of this paper, α could be labeled a variance component; however, α is often labeled a hyperparameter. However, no such parameter exists in the threshold model in [9] because both the mean and variance of y_i are jointly determined by η_i through p_i . For the normal likelihood in Equation [3], we might consider $\alpha = \sigma_e^2$. The joint posterior of all of the parameters for a more general GLMM could then be written as

$$\pi(\beta, \mathbf{u}, \sigma_u^2, \alpha | \mathbf{y}) \propto \pi(\mathbf{y} | \beta, \mathbf{u}, \alpha) \pi(\beta) \pi(\mathbf{u} | \sigma_u^2) \pi(\sigma_u^2) \pi(\alpha). \tag{15}$$

As with β , independent flat priors on σ_u^2 and α (or nonlinear functions thereof) might be specified; for example, $\pi(\sigma_u^2) \propto 1$ and $\pi(\alpha) \propto 1$, such that

$$\begin{aligned} & \pi(\beta, \mathbf{u}, \sigma_u^2, \alpha | \mathbf{y}) \\ & \propto \pi(\mathbf{y} | \beta, \mathbf{u}, \alpha) \pi(\mathbf{u} | \sigma_u^2) \\ & \propto \pi(\mathbf{y} | \beta, \mathbf{u}, \alpha) \exp\left(\frac{\mathbf{u}'\mathbf{A}^{-1}\mathbf{u}}{2\sigma_u^2} \right) (\sigma_u^2)^{-q/2}. \end{aligned} \tag{16}$$

This joint posterior density in Equation [16] is a general representation of an animal breeding GLMM when all parameters are unknown. Based on frequentist inference theory, [16] also represents the joint posterior density of \mathbf{y} and \mathbf{u} conditioned on β , σ_u^2 , and α ; [i.e., $\pi(\mathbf{y}, \mathbf{u} | \beta, \sigma_u^2, \alpha) \propto [16]$]; $\pi(\mathbf{y}, \mathbf{u} | \beta, \sigma_u^2, \alpha)$ is also labeled a penalized likelihood (4) or hierarchical likelihood (49). Maximum likelihood (ML) estimation of variance components and fixed effects requires integration of the random effects \mathbf{u} from $\pi(\mathbf{y}, \mathbf{u} | \beta, \sigma_u^2, \alpha)$ in order to derive the marginal likelihood $l(\beta, \sigma_u^2, \alpha | \mathbf{y}) \propto \pi(\mathbf{y} | \beta, \sigma_u^2, \alpha) = \int \pi(\mathbf{y}, \mathbf{u} | \beta, \sigma_u^2, \alpha) d\mathbf{u}$, which is distinct from the data likelihood function of, for example, [3] or [9]. This marginal likelihood is easily derived when $\pi(\mathbf{y} | \beta, \mathbf{u}, \alpha = \sigma_e^2)$ is Gaussian, as in [3], such that first- and second-derivative algorithms can be used to maximize $l(\beta, \sigma_u^2, \alpha | \mathbf{y})$ with respect to β and $\sigma' = [\sigma_u^2 \ \alpha]$ (70). The resulting estimates are then ML. However, for non-Gaussian $\pi(\mathbf{y} | \beta, \mathbf{u}, \alpha)$, as appropriate for discrete data analyses, this derivation is analytically intractable, and exact computations based on numeri-

cal quadrature are only possible in very specific situations (39). Therefore, several approximations to $l(\beta, \sigma_u^2, \alpha | \mathbf{y})$ based on quasi-likelihood theory have been suggested (4, 26, 71); the number of approximations seemingly have been dependent on the number of ways a nonlinear model can be linearized (59). Although such approximations may provide conceptually satisfactory solutions to the estimation of fixed effects and variance components, they do not necessarily provide a statistically logical framework for the prediction of genetic merits (47). Furthermore, inference based on ML is asymptotic, which is a nontrivial consideration in highly parameterized animal breeding models.

A more common method for the estimation of variance components in linear mixed models is REML because the resulting point estimates are generally less biased than ML estimates, particularly when $p = \dim(\beta)$ is large (70). The restricted likelihood of the variance components is equivalent to the following posterior marginal density (29):

$$\pi(\sigma | \mathbf{y}) = \iint \pi(\beta, \mathbf{u}, \sigma | \mathbf{y}) \mathbf{d}\beta \mathbf{d}\mathbf{u} \quad [17]$$

Similar to ML, REML estimates of σ are also modal estimates; that is, $\hat{\sigma} = \text{Arg}_{\sigma} \text{Max} \pi(\sigma | \mathbf{y})$. Analytical expressions for $\log \pi(\sigma | \mathbf{y})$ or the restricted log likelihood are easily attainable when the sampling distribution is Gaussian, as in Equation [3] (27, 70), but not otherwise. As with ML, several approximations to Equation [17] have been used to provide point estimates of variance. Although REML has often been used to describe the resulting estimates for variance components given non-Gaussian sampling densities (59, 71), animal breeders have typically referred to these estimates as marginal maximum likelihood (MML) (15, 36) to distinguish inference based on Gaussian likelihoods from inference based on non-Gaussian likelihoods. Prediction of breeding values and their standard errors of prediction are then generally based on empirical Bayes procedures, whereby $\tilde{\theta}_{\sigma}$ and $\hat{v}(\theta | \sigma, \mathbf{y}) \approx \tilde{\mathbf{H}}_{\sigma}^{-1}$ are computed as if $\sigma = \hat{\sigma}$, without accounting for the uncertainty on σ (15). Each of several methods based on MML are subsequently discussed.

The EM Method

The most common MML algorithm used thus far for threshold mixed models in animal breeding is the approximate expectation-maximization (EM)

method, which was proposed independently by Harville and Mee (30) and Stiratelli et al. (78). With \mathbf{u} as the missing data, the expectation step requires the computation of $E(\mathbf{u}' \mathbf{A}^{-1} \mathbf{u} | \sigma_u^2, \alpha, \mathbf{y})$. Because this computation is analytically intractable, a normality approximation on $\mathbf{u} | \sigma_u^2, \alpha, \mathbf{y}$ was suggested by Stiratelli et al. (78), which leads to an iterative expression for σ_u^2 closely resembling the REML EM algorithm:

$$\sigma_u^{2[t+1]} = \frac{\hat{\mathbf{u}}^{[t]'} \mathbf{A}^{-1} \hat{\mathbf{u}}^{[t]} + \text{trace}(\mathbf{A}^{-1} \mathbf{C}_{uu}^{[t]})}{q} \quad [18]$$

Here $[t]$ = algorithm iterate number, $\hat{\mathbf{u}}$ = random effects portion of $\theta^{[t]} = \text{Arg}_{\theta} \text{Max} \pi(\theta | \sigma_u^{2[t]}, \alpha, \mathbf{y})$, and \mathbf{C}_{uu} = random by random portion of $\tilde{\mathbf{H}}_{\sigma}^{-1}$ evaluated at $\hat{\theta}^{[t]}$. Further details on this algorithm are provided by Foulley et al. (15) and Hoeschele et al. (36). In simulation studies of threshold sire models using the EM method, Hoeschele et al. (36) and Simianer and Schaeffer (75) discovered significant empirical upward biases on MML estimates of variance components when subclass sizes were small; downward biases were typical in other closely related methods (4, 26). Moreno et al. (62) contended that the size and sign of the bias depended on the number of levels of fixed and of random effects relative to each other and to the size of the data file.

The Laplacian Method

Because of the computational burden in determining \mathbf{C}_{uu} for the EM algorithm, both Hoeschele et al. (36) and Foulley et al. (15) anticipated optimization routines that were analogous to derivative-free REML and avoided inversions of large matrices (27). Tempelman and Gianola (80) developed one such optimization method based on the use of the Laplacian method and in the context of a Poisson mixed model. The Laplacian approximation of the marginal density of the variance components is

$$\hat{\pi}(\sigma | \mathbf{y}) \propto \pi(\theta = \tilde{\theta}_{\sigma}, \sigma | \mathbf{y}) |\tilde{\mathbf{H}}_{\sigma}|^{-1/2} \quad [19]$$

such that the approximate MML estimate of σ corresponds to the mode of [19]. When $\pi(\mathbf{y} | \beta, \mathbf{u}, \alpha = \sigma_c^2)$ is Gaussian, as in [3], then these estimates are REML. Note that [19] is simply [15] evaluated at $\tilde{\theta}_{\sigma}$ and has a determinant-based adjustment of $|\tilde{\mathbf{H}}_{\sigma}|^{-1/2}$. Use of sparse matrix methods (66) generally makes it easier

TABLE 1. Empirical relative bias of threshold model marginal maximum likelihood (MML) and REML estimates of sire variance estimates based on 30 replicates of each population.

Method	Population 1	Population 2	Population 3
	(%)		
REML ¹	-0.61	0.47	0.70
EM ² MML	-47.65**	-43.04**	-14.94**
Laplacian MML	-4.57	-9.04	0.39

¹Analysis of underlying variate.

²Expectation-maximization.

** $P < 0.01$.

in single-trait models to compute $|\hat{\mathbf{H}}_{\sigma}|^{-1/2}$ than $\hat{\mathbf{H}}_{\sigma}^{-1}$, which is needed to determine \mathbf{C}_{uu} in the EM algorithm. If more than one variance component is to be estimated, multidimensional search algorithms can be used (61).

Unlike the previous contention of Tempelman and Gianola (80), the EM and the Laplacian approximations are not equivalent; that is, MML estimates may differ substantially between the two methods. According to Carlin and Louis (5), the Laplacian method has an approximation error that decreases with $n^{-3/2}$ compared with $n^{-1/2}$ for the EM method as the sample size n increases. The difference in these approximation errors can be demonstrated in the following threshold sire model simulation study. Three different populations were defined by different true values of sire variance (σ_s^2) and average sire family sizes (n_s): population 1, $\sigma_s^2 = 0.05$, $n_s = 20$; population 2, $\sigma_s^2 = 0.10$, $n_s = 20$; and population 3, $\sigma_s^2 = 0.10$, $n_s = 60$. In all populations, half-sib progeny were generated from 250 sires and were randomly assigned over 500 herds and five levels of a fixed effect with equally spaced effects of 0.5 on the underlying scale. Herd effects were independently drawn from $N(0, 0.20)$, and herd variance was presumed to be known to limit the computational dimension of the problem. An overall liability mean of $\mu = \Phi^{-1}(0.9375)$ was used to generate a mean rate for disease incidence of roughly 6.25%, ignoring the attenuating effect of the sire variance on marginal mean responses. The REML estimates of sire and residual variance components were also computed for the underlying liability variates as a control. Based on 30 replicates for each population, relative biases for the two MML estimators (empirical bias divided by σ_s^2) and the REML estimator based on the underlying liability variates are presented in Table 1. In all cases, the EM method led to MML estimates of sire variance that were significantly biased downward, particularly with

small sire variances and small average family sizes. However, no significant empirical bias was associated with the Laplacian MML estimates.

Except in quasi-likelihood settings (71), there is no readily known EM method for estimating the overdispersion parameter α or other hyperparameters in GLMM that are more complex than the threshold mixed model. Therefore, the Laplacian method has been a particularly useful alternative for hyperparameter estimation in negative binomial mixed models (83), Weibull mixed models (10), and outlier-resistant mixed linear t models (79). Another advantage of the Laplacian method over the EM method is the ability to generate the estimated marginal posterior density $\hat{\pi}(\sigma|\mathbf{y})$ from a grid of points (10) and to provide interval estimates for the dispersion parameters or likelihood ratio hypothesis tests on elements of σ . Alternatively, the curvature from $\log\pi(\sigma|\mathbf{y})$ can be used to estimate a standard error for these variance components, a practice that has been implemented in derivative-free REML implementations (27). However, these standard errors are appropriate only if $\hat{\pi}(\sigma|\mathbf{y})$ or profile plots thereof are reasonably symmetric.

Markov Chain Monte Carlo Methods

Bayesian methods are being increasingly applied to statistical genetic inference in animal breeding, partly because of increased computing power and the availability of recently developed inference algorithms based on simulation. The most popular family of such algorithms is Markov Chain Monte Carlo (MCMC), which includes Gibbs sampling. Gibbs sampling requires knowledge about the full conditional densities (FCD) of all of the unknown parameters in the model. These FCD are easy to derive in linear mixed effects models (19, 92). The MCMC was first applied to GLMM by Zeger and Karim (95), who recognized that not all FCD are easily recognizable and in those cases used rejection sampling methods that were computationally onerous. This problem was eventually alleviated by a data augmentation step for threshold mixed models by Albert and Chib (2), thereby inspiring the first Gibbs sampling application to GLMM in animal breeding by Sorenson et al. (77). This data augmentation step involves generating the underlying liabilities l_i ; $i = 1, \dots, n$, as previously discussed. Subsequent sampling procedures of other FCD within the same Gibbs cycle are then identical to those specified for linear mixed

effects models. For the most part, Gibbs sampling has been the only MCMC method considered thus far in animal breeding. Despite its elegance, however, Gibbs sampling is somewhat restrictive in terms of the class of models that can be investigated in animal breeding because the FCD of all the parameters must be known. In more general models, Metropolis-Hastings steps for nonrecognizable FCD may be particularly useful within a broader Gibbs sampling scheme (7, 82, 85). Furthermore, as advocated by Carlin and Louis (5), Metropolis-Hastings sampling is easier to implement than various rejection sampling schemes and, with proper tuning, leads to faster MCMC mixing, which is synonymous with greater precision on estimated densities for the same length of the MCMC chain.

There are other MCMC-derivative methods that might be applied to the estimation of variance components in GLMM. One is the use of MCMC to provide maximum likelihood or restricted (marginal) maximum likelihood estimates of the variance components as described by McCulloch (58). Another derivative method makes use of an iterative bootstrap bias correction of Kuk (48), which has been implemented in animal breeding by Moreno et al. (62).

MULTIPLE-TRAIT MODELS

Multivariate multiple-trait models, involving the modeling of two or more types of traits simultaneously, are important, particularly in selection situations in which the data are not necessarily missing at random. If genetic progress from selection is to be attained, livestock of lower genetic merit for economically important traits should be culled much more frequently than at random. Multiple-trait mixed models have been used as a tool to correct the resulting selection bias on estimation and prediction through the use of traits that might be measured on all or most individuals. For example, genetic and residual correlations can be modeled between first lactation milk production and subsequent fertility measures to correct for biases that result from missing fertility data because of involuntary culling. Although predictions for multiple-trait mixed models have been derived under a BLUP context for multivariate normality on all sampling distributions (34), GLMM involving different classes of traits have been generally developed following Bayesian ideas. One particularly important application involves the joint analysis of continuous and binary or ordinal categorical traits (76, 87). In a multivariate continuous-discrete model, the continuous trait may provide a

substantial increase in the amount of information on genetic predictions for the discrete trait if the genetic or residual correlations are large and progeny groups are small. For example, the accuracy of genetic evaluations on calving ease in cattle may increase by 15 to 30% in a multiple-trait analysis with birth weight (41). These multivariate models may provide the methodological foundation for fundamental knowledge on the genetic and physiological relationships between discrete fitness or fertility and continuous production traits or physiological indicators in livestock. Multiple-trait models have also been developed for the joint analysis of two or more binary traits (17) and one count and one binary trait (14).

Estimation of dispersion parameters in multiple-trait GLMM is more challenging than in univariate mixed models, because of the greater dimensionality of multiple-trait genetic evaluation systems. However, another difficulty appears to be manifested by a popular strategy of hybrid estimation for dispersion parameters considered thus far in animal breeding (38, 41, 75). In this procedure, genetic parameters are estimated marginally as in Equation [17]; however, the residual regression or correlation parameter between any two traits is estimated jointly with the vector of location parameters in a manner that is analogous to ML estimation. Based on empirical simulation studies, the ML estimates of these residual parameters tend to be characterized as having greater bias problems than do the MML estimates of the genetic parameters (54, 75). A fully marginal procedure based on Gibbs sampling to infer upon all parameters in a bivariate threshold linear mixed model has been proposed by Jensen (43) and recently applied by Jorgensen and Madsen (44). Further research development on multiple-trait GLMM methodology is desired.

CENSORED DATA MODELS

Threshold mixed models may be particularly useful for the genetic analysis of longevity or stayability to an arbitrary age (89) or rates of nonreturn to estrus (93). However, expression of such traits on a binary scale, when the data are recorded on a continuous scale, represents a potentially substantial loss of information. These data may be analyzed more appropriately using censored models, such as the one developed for animal breeding by Carriquiry et al. (6). Some censored models also allow for time-dependent covariates, as illustrated in an application of the Weibull mixed model to dairy cattle longevity by Ducrocq and Casella (10). Gibbs sampling im-

plementations of censored linear mixed models are particularly tractable (20); Gibbs sampling implementations of survival models to animal breeding data have recently been developed by Korsgaard et al. (46). Weller and Ron (93) argued that a normal distribution, such as that specified in [3], is not appropriate for days open. However, other sampling distributions for continuous GLMM, such as gamma, log-normal, or inverse Gaussian distributions (57), may be viable alternatives.

Censoring may be a consideration that is as important for analyzing discrete fertility data as it is for continuous data. Previous studies on estimating genetic variances for number of AI services until conception have routinely deleted records that have no corresponding subsequent calving date, which may account for 20% of all data edits (28). Assuming such edits correspond to animals with poor fertility, the selection bias would likely generate a downward bias on the estimates of genetic variance based on results and arguments presented by Carriquiry et al. (6). However, it is also known that higher producing cows are likely to be afforded greater opportunity to have multiple AI services such that estimated genetic variance for number of AI services might be somewhat confounded with genetic variance for milk production. Furthermore, as indicated by Raheja et al. (67), breeding high producing cows more frequently than low producing cows could cause a false estimated spurious antagonism between production and reproduction in a multiple-trait analysis. A bivariate normal Poisson model that allows for censoring on counts would appear to be a viable alternative model for the joint analysis of milk production and number of AI services until conception. Gibbs sampling implementations of censored versions of ordinal categorical models are also possible (20) and may be particularly useful for the analysis of unobserved calvings relative to observed calvings in a genetic evaluation system for dystocia (3).

GENERALIZED LINEAR ANIMAL MODELS

It is conceptually advantageous to specify the second-stage prior $\pi(\mathbf{u} | \mathbf{G})$ in [2] as Gaussian in most GLMM to allow the modeling of complex interdependence between levels of the random effects (e.g., those from genetic relationships). Mathematically convenient or conjugate priors have been considered for modeling sire or herd effects in threshold models (16) and in Weibull mixed models (10); however, levels of random effects must be specified to be a priori independent in such cases. Despite the conceptual de-

velopment of generalized linear animal models, where \mathbf{u} in [16] represents breeding values of individual animals (rather than transmitting abilities of sires) and \mathbf{A} represents the additive genetic relationships between these animals, most applications of GLMM in animal breeding have been on the basis of a sire model. Part of the reason for this emphasis may be the large empirical biases of variance component estimates observed in simulation studies using a threshold sire model, implying that this problem would be more acute in animal models. This problem was further manifested by Mayer (56), who indicated that threshold animal models and threshold sire models are not equivalent, as they are in linear mixed models. More specifically, he found that, for half-sib family structures, MAP estimates of sire breeding values based on threshold sire models were much closer to the posterior means of these breeding values than the corresponding MAP estimates based on threshold animal models. This discrepancy is particularly significant because posterior means provide an optimal selection rule in truncation selection (11).

The MML estimation of genetic variance of litter size under Poisson mixed models were recently found to be problematic in both sire model (65) and animal model (55) implementations. These results were in contrast to results of a simulation study that indicated good frequentist properties of the Laplacian MML estimator and slight downward biases on EM MML estimates of genetic variance in Poisson animal models (81).

Simulation Study

A simulation study was designed to illustrate the frequency properties of EM and Laplacian estimates of genetic variance under a threshold animal model. An animal model was used to generate binary data (e.g., incidence of clinical mastitis in dairy cows). Data for 1280 dams and their female offspring were generated from Bernoulli distributions with parameters $p_{ijk} = \Phi(\eta_{ijk})$ where $\eta_{ijk} = \mu + f_i + h_j + a_k$. Here μ = overall mean, $f_i = -1 + 0.5(i - 1)$ for $i = 1, 2, \dots, 5$ denotes a fixed effect with five levels, $\mathbf{h} = \{h_j\} \sim N(\mathbf{0}, \mathbf{I}_h^2)$ is a 64×1 vector of herd effects, and $\mathbf{a} = \{a_k\} \sim N(\mathbf{0}, \mathbf{A}\sigma_a^2)$ is a 1344×1 vector of random additive genetic effects. The Bernoulli parameter p_{ijk} denotes the expected probability of no infection for the individual k with location parameter η_{ijk} . The base population consisted of 64 unrelated sires without records and 256 unrelated dams with records. Dams were nested within herd, and each herd contained 4

dams. Sires were randomly mated to dams to generate a total of 1024 female progeny, and each progeny was located in the same herd as her dam. Levels of the fixed effect were randomly assigned to both dams and progeny in generating the records. Three populations pertaining to different values of the additive genetic variance σ_a^2 were considered: population 1, $\sigma_a^2 = 0.20$; population 2, $\sigma_a^2 = 0.60$; and population 3, $\sigma_a^2 = 1.00$. For all populations, $\sigma_h^2 = 0.40$, such that the heritabilities on the liability scale for the three populations were 0.13, 0.30, and 0.42. Each of the populations were further considered at four different environments or values of the overall mean: $\mu = \Phi^{-1}(0.50)$, $\mu = \Phi^{-1}(0.65)$, $\mu = \Phi^{-1}(0.80)$, and $\mu = \Phi^{-1}(0.95)$. These different values roughly represent different levels of overall liability or, equivalently, expected rates of infection of 50, 35, 20, and 5%, respectively, ignoring the attenuating effect of the variance components on these rates. The MML estimates were computed using the EM and Laplacian methods. Fifty replicates of each population for each of the four different values of μ were used to assess the empirical bias and empirical error (root mean square error) of the estimates; both measures were expressed on a relative basis (i.e., as a percentage of the true variance component).

Because the relative performance of both methods did not vary greatly over all three populations, only

results for population 2 are visually presented. Empirical relative biases and empirical relative errors of the two approximate methods for variance component estimates are given in Figures 1 and 2, respectively, for population 2. In general, the relative biases for the Laplacian estimates of σ_h^2 were negative but small, except for population 3, for which the relative biases were as large as -20%. In contrast, estimates of σ_h^2 under the EM method showed large negative biases -15 to -45% that generally increased as σ_a^2 increased (i.e., from population 1 to population 3). There were no trends in relative biases for σ_h^2 estimates over increasing $\Phi(\mu)$ for either the EM or the Laplacian method within each population, except for an unexpected decrease in bias for Laplacian estimates at the most extreme incidence level within the first two populations. The differences between empirical relative errors of σ_h^2 estimates for the two methods remained somewhat constant over increasing $\Phi(\mu)$ within each population; however, these differences widened as the true values of σ_a^2 increased.

Estimates of genetic variance were always characterized by larger relative bias and relative error than estimates of herd variance. The Laplacian estimates of σ_a^2 were biased -20 to -50%, and absolute bias increased with σ_a^2 . Empirical relative biases on EM

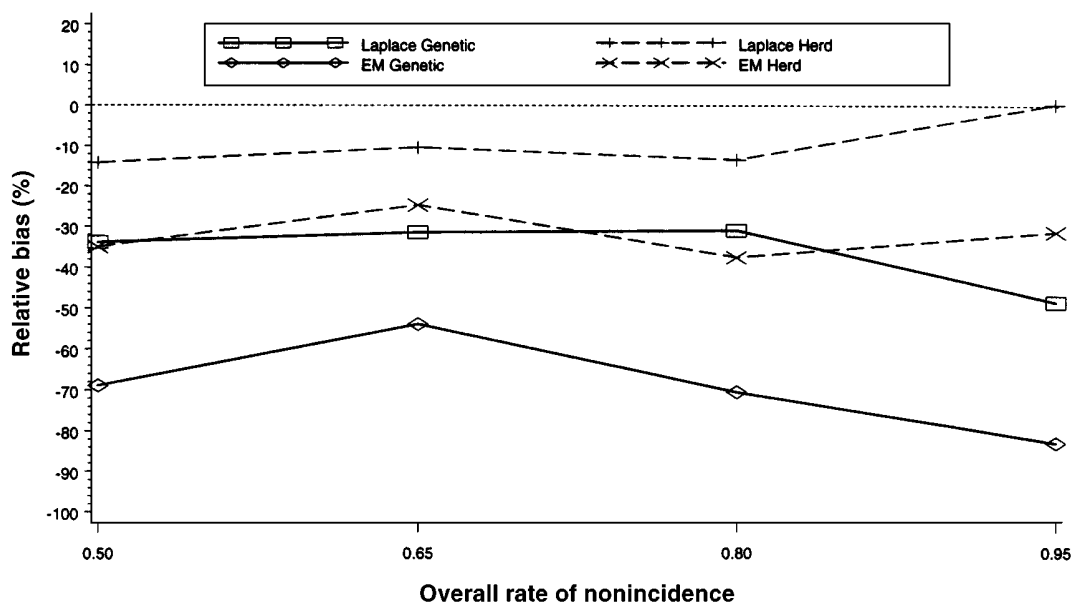


Figure 1. Empirical relative bias (based on 50 replicates) of herd and genetic variance component estimates using either the Laplacian method or expectation-maximization (EM) in an animal model simulation study. Animal variance = 0.60; herd variance = 0.40.

based estimates of σ_a^2 were substantially larger than the Laplacian estimates, ranging from -50 to -80%, and also increased in absolute measure with σ_a^2 . Relative biases were somewhat proportional to $\Phi(\mu)$ or increasing extremity in incidence rates. Larger relative errors for estimates of σ_a^2 were also associated with larger $\Phi(\mu)$ for both methods, although relative errors showed no trend with σ_a^2 . Nevertheless, the Laplacian method generally yielded estimates with 20 to 30% less relative error than EM.

Marginal modal estimates of variance components based on the Laplacian method versus Gibbs sampling were compared in another simulation. Because of the computational expense of MCMC in GLMM, only two data files based on the simulation procedure just described were investigated. The overall liability mean considered in both data files was $\mu = \Phi^{-1}(0.80)$. The first data file was generated with a genetic variance $\sigma_a^2 = 0.20$ and the second data file was generated with $\sigma_a^2 = 1.00$. For both data files, $\sigma_h^2 = 0.40$ and was presumed known in order to allow a direct comparison of univariate marginal inference on σ_a^2 . A proper prior yet highly dispersed inverted gamma density on σ_a^2 was used for both data files. In data file 1, the prior mean, mode, and standard deviation of σ_a^2 were 0.075, 0.025, and 2.23, respectively. In data file 2, the prior

mean, mode, and standard deviation on σ_a^2 were 0.75, 0.25, and 23.69, respectively. Proper prior densities on variance components were used to ensure a proper full joint posterior density (64). Starting from the MML of σ_a^2 and MAP of θ , a total of 5000 samples from each conditional distribution in a Gibbs cycle was generated before samples were collected. Based on trajectory plots of MCMC samples of σ_a^2 versus MCMC cycles, this preliminary sampling ensured the necessary burn-in required for convergence to the equilibrium joint distribution in the Gibbs sampler (5, 19). For data file 1, 200,000 samples were generated, and every second sample was saved for a total of 100,000 Gibbs samples. This was necessary to generate an effectively large enough number of samples because of the stickiness of the chain, particularly when variance components are small. For data file 2, 100,000 samples were generated with every second sample saved for a total of 50,000 samples. Both sampling strategies were designed to compromise computing time with hard disk space economically. Posterior densities were generated using the Rao-Blackwellization method (19). A flat uniform prior on σ_a^2 was also used in the Laplacian method for further assessment of the impact of the informative and proper inverted gamma prior on the posterior density.

Figure 3 shows the posterior densities of the genetic variance component for data file 1 ($\sigma_a^2 = 0.20$)

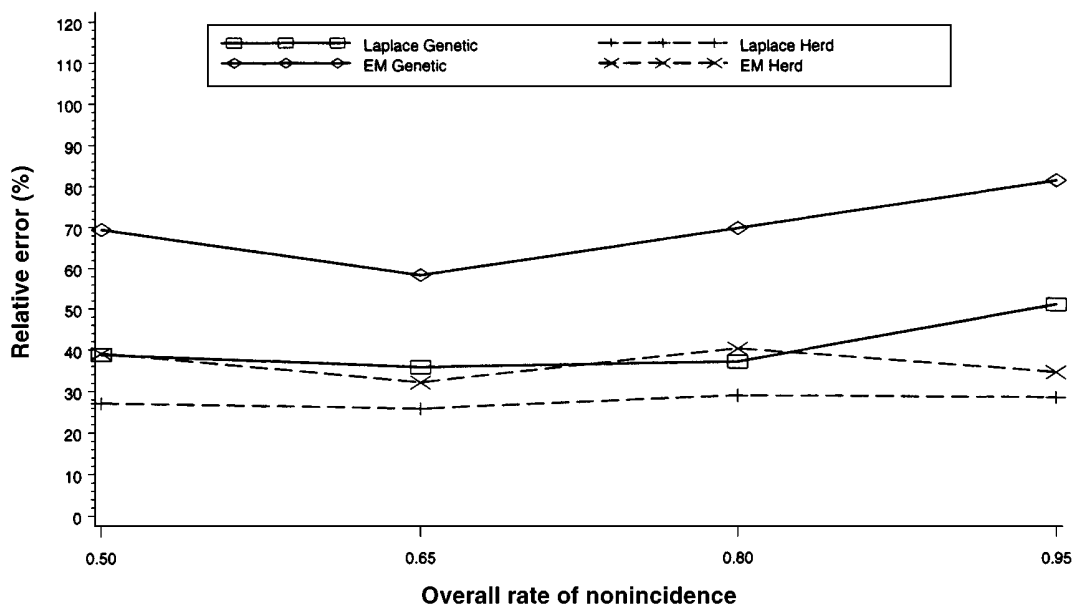


Figure 2. Empirical relative error (based on 50 replicates) of herd and genetic variance component estimates using either the Laplacian method or expectation-maximization (EM) in an animal model simulation study. Animal variance = 0.60; herd variance = 0.40.

under both Laplacian and Gibbs sampling inference. In addition, the prior density used in deriving both posterior inferences is shown for comparison. The modes (-0.03) of both posterior densities are virtually identical and may have been strongly influenced by the prior density on σ_a^2 , which has a mode at 0.025. However, the right tail of the posterior density under Gibbs sampling was much heavier than that derived under Laplacian integration. This heavier tail resulted in a larger posterior mean (relative to the posterior mode) of 0.119 and a posterior standard deviation of 0.102 under Gibbs sampling. The Laplacian density based on a flat variance component prior was more dispersed than the other posterior densities with a mode near 0.18. Because a seemingly highly dispersed prior influences the posterior density relative to a flat prior specification, this data may not be too informative for inference on σ_a^2 .

Figure 4 displays posterior marginal inferences for data file 2 ($\sigma_a^2 = 1.00$). The Laplacian modal estimates under both informative and flat priors are highly biased downwards, which is consistent with the increasing relative bias of modal estimates found with larger values of σ_a^2 in the simulation study results with the EM versus Laplacian comparisons. Further, there appears to be a relatively minor effect of the prior on posterior inference, which is again

shown in the two Laplacian posterior densities for which the difference in the two modes was relatively small. The posterior density generated under Gibbs sampling had a mode near 0.90, a mean of 0.973, and a posterior standard deviation of 0.363.

Leonard et al. (50) indicated that the Laplacian approximation would be remarkably accurate when $\pi(\theta|\sigma, \mathbf{y})$ is approximately normal but would tend to inadequately approximate the tails of the marginal density. This lack of accuracy was apparent in Figures 3 and 4; the tails of the Laplacian density were appreciably lighter than the Gibbs-derived density. In Figure 3, the true (Gibbs) and approximate (Laplacian) marginal modes almost directly correspond, but a wide discrepancy exists between the two modes in Figure 4. Hoeschele et al. (36) thought that the empirical bias problem of EM estimators resulted from the normality approximation invoked in the expectation step. However, from the comparisons of marginal densities derived by the Laplacian method and those derived by the MCMC method (Figures 3 and 4), part of the problem in bias estimation using approximate MML apparently stems from the choice of a point estimator (i.e., posterior mode rather than mean or median) in addition to the normality approximation invoked on the posterior distribution of the location parameters. The most appropriate estimator depends on the choice of a loss function, which is an ambiguous exercise at best; therefore,

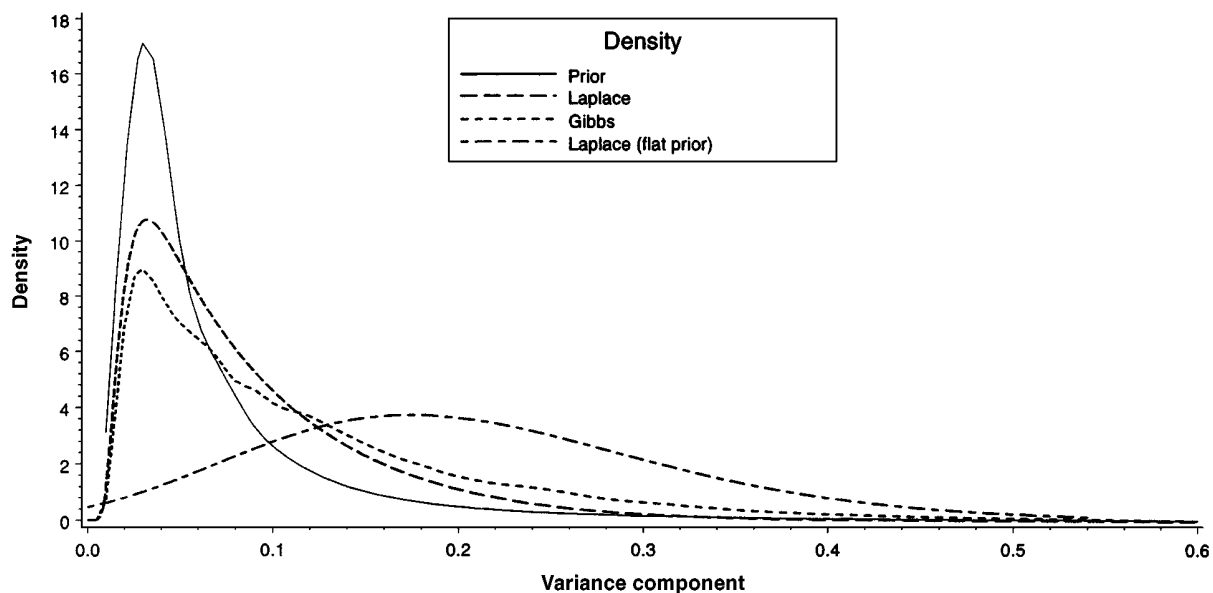


Figure 3. Prior and posterior marginal densities of σ_a^2 under the Laplacian method and Gibbs sampling for stimulated data file 1 (herd variance = 0.40 presumed known; animal variance = 0.20).

interval estimation of σ seems advisable. The utility of approximate MML methods such as the Laplacian and the EM algorithms clearly rely on the closeness of $\pi(\theta|\sigma, \mathbf{y})$ to normality; this deviation from normality would appear to be greatest with small subclass sizes, larger variances, and larger dimensions of \mathbf{u} . With regard to the latter, the EM or Laplacian approximation for $\hat{\pi}(\sigma|\mathbf{y})$ is poorer if the dimension of \mathbf{u} to be integrated out is larger (i.e., in animal models) than it might need to be (i.e., in sire models) for half-sib population structures. In a sire model application to data with seven ordinal categories, Sorensen et al. (77) found no discrepancy in MCMC-based and ML point estimates of σ_u^2 . However, sire model parameterizations can be advocated only for population structures that are dominated by half-sib relationships; this situation is increasingly unlikely with emerging reproductive technologies. Therefore, it seems necessary that inference on genetic parameters of GLMM should be based on MCMC to accommodate biologically realistic animal models. Hoeschele and Tier (37) compared point estimates based on MCMC against EM estimates and reached similar conclusions. Approximate MML estimates of variances and the empirical Bayes solutions of location parameters that are based upon them, nevertheless, do provide valuable starting values for a single MCMC chain in terms of minimizing burn-in.

Generalized linear animal models are also plagued by extremely slow mixing in MCMC implementations.

In particular, single-component updating in Gibbs sampling leads to very slow mixing in linear animal models (92), which is further intensified in generalized linear animal models (37). For example, Hoeschele and Tier (37) determined that over 200,000 MCMC samples were required to attain less than 1000 effectively independent samples based on the time-series methods discussed by Geyer (21). In our study, the number of effectively independent samples for σ_u^2 was 223 in data file 1 and 325 in data file 2 using Geyer's methods. The lack of convergence on one parameter (e.g., σ_u^2) could lead to false inferences concerning the other parameters (e.g., β or \mathbf{u}) that appear to have converged. Greater efficiency of implementations of MCMC methods in generalized linear animal models requires further mathematical and algorithmic insights.

Proper priors have been advocated for linear mixed models (35) and appear to be particularly critical for MCMC implementations in generalized animal models. Hoeschele and Tier (37) determined that with flat noninformative priors on σ_u^2 , as implied in [16], the Gibbs samples for σ_u^2 strayed toward infinity. The same phenomenon was experienced in our simulation study before the decision was made to impose proper priors. These priors may be diffusely specified but not to the point that computer round-off error leads to an effectively flat prior.

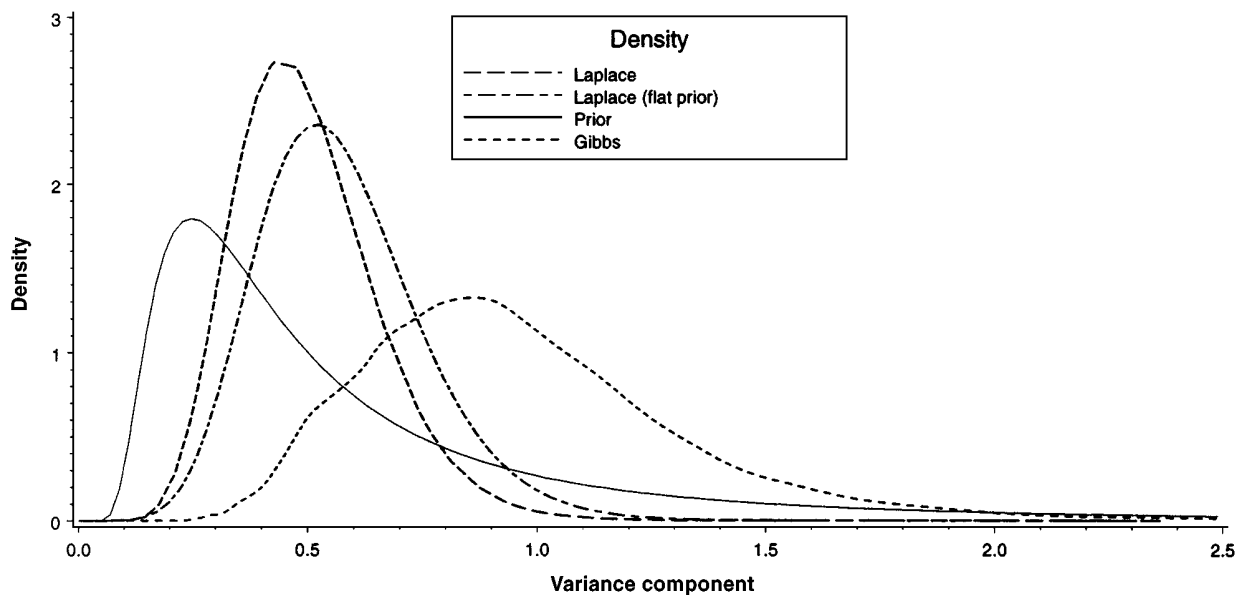


Figure 4. Prior and posterior marginal densities of animal variance under the Laplacian method and Gibbs sampling for simulated data file 2 (herd variance = 0.40 presumed known; animal variance = 100).

RANDOM VERSUS FIXED HERDS

Historically, animal breeders have treated contemporary groups such as herd-year-seasons as fixed effects. Arguably, contemporary groups could and should be treated as random or exchangeable except that Henderson (32) warned about a form of prediction bias on genetic effects when contemporary groups and genetic values are positively correlated. However, simulation studies suggest that treating contemporary groups as random rather than as fixed leads to genetic predictions with much better frequentist performance, even when positive correlations exist between contemporary groups and genetic values (90). Differences in rankings in estimated breeding values of sires have also been observed with field data (9) and naturally have implications for variance component estimation. Also, treating contemporary groups as fixed negates the possibility of modeling autoregressive (91) or other temporal correlation structures over sequential year-seasons. In some simulation studies used to assess the frequentist properties of the EM MML estimator of genetic variance, herds have been generated according to a random process but then analyzed as if they were fixed (36, 75). In these cases, significant empirical biases on σ_u^2 have often tended to be upward, but downward biases were found when herds were treated as random (Figure 1). Hoeschele and Tier (37) also noted that point estimates of variance components based on MCMC had better frequency properties when herds were treated as random than when herds were treated as fixed. This situation is not too surprising because the borrowing of information from across random herds enables the effective number of records or progeny for each animal to increase, thereby leading to more efficient variance component estimation. However, recent work by Moreno et al. (62) appears to indicate serious deficiencies with interval coverage of marginal densities based on MCMC, even with randomly specified herds. Those researchers alleviated this problem using the iterative bootstrap correction method of Kuk (48). The results of Moreno et al. (62) are baffling in light of the general understanding that Bayesian estimators have excellent frequentist properties, are admissible, and are better than estimates generated by frequentist or likelihood approaches (5). In the study by Moreno et al. (62), herds were generated from a uniform distribution but analyzed as if they were Gaussian.

Treating herds as random also alleviates the extreme category problem (**ECP**) discussed by Misztal et al. (63). An ECP occurs when all individuals in a

contemporary subclass (e.g., herd-year-season) have the same extreme response (e.g., all cows are healthy, or all cows have no assistance on calving); treating these subclasses as fixed effectively leads to their deletion in statistical analysis. Hoeschele and Tier (37) discovered that placing wide uniform bounds on herd effects did not alleviate the ECP problem in a MCMC analysis.

Treating effects as random tends to lessen the impact of model misspecification and serves to make the statistical analysis more robust (53). Therefore, treating contemporary subclasses as random seems advisable to allow useful implementations of generalized linear animal models in genetic evaluation systems, particularly when disease incidences are extreme in a threshold mixed model analysis or mean responses are low in a Poisson mixed model analysis.

EXTENSIONS OF THE GENERALIZED LINEAR MIXED MODEL

Perhaps the most appealing feature of hierarchical Bayes models is the possibility of modeling greater complexity by utilizing auxiliary variables embedded in additional (i.e., fourth or fifth stage) hierarchical prior specifications rather than dealing directly with complicated marginal sampling distributions. That is, it is possible to account for uncertainty of the submodel by nesting the sampling distribution of the data within a more broadly classified model (1). These multiple-stage models have provided new opportunities for quantitative genetic analysis, particularly for problems requiring complex dispersion specifications. The MCMC implementations are particularly helpful in accounting for the propagation of uncertainty throughout the various stages of these models. Some examples are discussed subsequently.

Overdispersed Count Data

Foulley et al. (14) first introduced the Poisson mixed model for the analysis of count data in animal breeding. However, a higher order hierarchical Bayes model based upon a gamma mixture of Poisson distributions allows a more general model. This model was the basis for the negative binomial mixed model of Tempelman and Gianola (83), who were concerned about the inability of the Poisson mixed model of Foulley et al. (14) to account adequately for extra Poisson residual variation that could be characterized by an overdispersion parameter α . In an application to the number of AI services required for conception in dairy cows, Tempelman and Gianola (83) noted that the mode of the marginal posterior distribution

of the genetic variance was 20 times larger in a Poisson mixed model that did not account for overdispersion than in a negative binomial mixed model that incorporated overdispersion. Apparently, a large posterior correlation existed between the overdispersion parameter and genetic variance in their negative binomial model, thereby causing the large discrepancy between estimates of σ_u^2 by the two models. The negative binomial mixed model has been implemented with little success in the MML estimation of genetic variance of litter size in sheep (55). Reasons may include inappropriate distribution or model specification, impropriety of the joint posterior, or a data structure that does not allow a good approximate MML or empirical Bayes analysis. Recently, Tempelman (82) applied a Metropolis-Gibbs sampling approach to similarly overdispersed Poisson mixed effects model analysis of litter size in Iberian pigs.

Heterogeneous Dispersion Parameters

Heterogeneous genetic and residual variances across contemporary management groups appear to be common for quantitative traits of livestock. Ignoring these variances can lead to appreciable bias in estimated breeding values (88). It seems logical to model unequal variances in much the same way as unequal means are modeled, that is, through a structural modeling approach (69). Here, the logarithms of the residual and random effect variances are expressed as linear functions of fixed (i.e., with flat priors) and random effects in a secondary stage of the hierarchical model. Early research in animal breeding of heterogeneous variances involved computing separate estimates of σ_e^2 and σ_u^2 for each management group, which often lead to many 0 estimates of σ_u^2 , as very limited information is provided by each group separately. In contrast is the elegance of a hierarchical Bayes approach, whereby the specification of random contemporary group effects on the log variances allows the borrowing of information from all groups for estimating genetic or residual variances within each single contemporary group. This shrinkage of variances is also described in a hierarchical Bayes model for Gaussian data developed by Gianola et al. (24). San Cristobal et al. (69) specify secondary model stages for log variances as follows:

$$\gamma_{e_j} = \ln(\sigma_{e_j}^2) \sim \pi(\gamma_{e_j} | \mu_{e_j} = \mathbf{p}'_{e_j} \delta_e, v_e) \quad [20a]$$

and

$$\gamma_{u_j} = \ln(\sigma_{u_j}^2) \sim \pi(\gamma_{u_j} | \mu_{u_j} = \mathbf{p}'_{u_j} \delta_u, v_u) \quad [20b]$$

where j is the contemporary subclass (i.e., herd) indicator, and $\omega_{u_j} = \gamma_{u_j} - \mu_{u_j}$ and $\omega_{e_j} = \gamma_{e_j} - \mu_{e_j}$ are typically specified to have inverted gamma distributions with degrees of freedom v_u and v_e , respectively. The means, μ_{e_j} and μ_{u_j} , of the log variances for subclass j are then specified to be linear functions of causal factors δ_e and δ_u through known incidence vectors \mathbf{p}'_{e_j} and \mathbf{p}'_{u_j} . Foulley and Gianola (13) have recently developed similar procedures for threshold model analyses of ordinal categorical data with the restriction that the data cannot be binary. In an application to calving difficulties in American Simmentals, they (13) determined that residual variances on the underlying liability scale increased as age of dam increased, allowing a substantial improvement in fit over a highly parameterized threshold model that ignored heteroscedasticity. This modeling framework could also be extended to multiple-trait GLMM using a Metropolis-Hastings step within a broader Gibbs sampling analysis. For example, the residual regression parameter of the bivariate linear threshold model (41), in a joint analysis of milk production and conception rate, could very well depend on herd management; that is, greater residual antagonism between production and fertility might be anticipated in poorly managed herds than in well-managed herds. This antagonism could be modeled as a fourth- or fifth-stage specification in a hierarchical Bayes model by specifying the residual regression parameter for each herd to be a random variable from some prior distribution.

t Models

Hierarchical models may also be useful for muting the effect of outlier residual or random effects, alleviating somewhat the pervasive problem of tampered records because of preferential treatment of livestock by individual breeders or owners. Let the sampling distribution be Gaussian as in [3] except

that $\mathbf{R} = \text{diag}\left(\frac{\sigma_e^2}{\lambda_i}\right)$ where λ_i is specific to observation i .

We might rewrite [3] to denote this conditioning; that is, $\pi(\mathbf{y} | \beta, \mathbf{u}, \sigma_e^2, \lambda)$ where $\lambda = \{\lambda_i\}$. Then, a second-stage specification might be that $\lambda_i, i = 1, 2, \dots, n$ are a priori independent with density $\pi(\lambda | \mathbf{v}) = \prod_{i=1}^n \pi(\lambda_i | \mathbf{v})$ where \mathbf{v} = hyperparameter structuring this prior density. The marginal distribution or likelihood of the data is then

$$\pi(\mathbf{y} | \beta, \mathbf{u}, \sigma_e^2, \nu) = \int \pi(\mathbf{y} | \beta, \mathbf{u}, \sigma_e^2, \lambda) \pi(\lambda | \nu) d\lambda. \quad [21]$$

For example, if $\pi(\lambda | \nu)$ is gamma or exponential, then [21] is Student's t or double exponential, respectively. This second component, $\pi(\lambda | \nu)$ in [21], allows specification of a marginal error distribution that is heavier tailed and, hence, more resistant to outliers than is the normal distribution (5). The third stage of a complete model would be defined by $\pi(\mathbf{u} | \sigma_u^2)$, and the final fourth stage would be defined by $\pi(\sigma)$. Applications to the genetic analysis of milk production is provided in Strandén (79).

The marginal prior density of the genetic effects could be specified in a similar way. A dilemma, nevertheless, seems to arise here. Animal breeders want to be able to identify and utilize genetic outliers while muting residual outliers. Genetic outliers under the linear additive genetic model may result from major gene or nonadditive genetic effects.

Foulley and Gianola (13) indicated that their heteroscedastic threshold model is a special case of a threshold t model in which an overall mean is only modeled in δ_e or δ_u of [20]. Threshold t models were introduced by Gianola and Sorensen (25) and may have particular merit for subjectively scored ordinal traits such as dystocia or body condition.

Segregation and Linkage Analysis

The current conventional wisdom in animal breeding dictates that many traits are genetically influenced by a large number of loci of minor effect and a small number of loci with major effects. The model in Equation [16] only allows for the former. Segregation and linkage analyses extends this model to allow inference on major gene effects. A threshold model allowing segregation analysis for animal breeding has recently been introduced by Thaller et al. (84). Genetic parameters were estimated using maximum likelihood in a model that did not allow for relationships between parents. Recently, Janss et al. (42) applied Gibbs sampling to complex segregation analysis for normally distributed production traits based on an animal model. Their strategy could be also applied to non-Gaussian GLMM for segregation analysis, although computational challenges would not be trivial for binary data in light of the mixing problems faced by Janss et al. (42). With marker information, potentially sharper inference and better Gibbs sampling mixing would be allowed in a linkage analysis relative to segregation analysis. The MCMC strategy

developed for linkage analysis in continuous production traits by Uimari et al. (86) for the model of Fernando and Grossman (12) could be extended conceptually to inference based on GLMM for discrete fitness and fertility traits.

CONCLUSIONS

Generalized linear mixed models have been used in dairy cattle breeding because of the increasing emphasis on fitness and fertility. Implementations of GLMM are not much more difficult than regular linear mixed model analyses as equation structures are similar. Despite the worldwide adoption of animal models for genetic evaluations, however, sire model implementations predominate for GLMM. In half-sib populations, joint posterior modal estimates of breeding values may deviate more from the corresponding posterior means under animal model versus sire model parameterizations. However, implementations of animal model GLMM are needed as population structures become increasingly complex and as marker information accumulates for research on inheritance modes. If approximate methods for inference on genetic parameters are needed, the Laplacian method should be chosen over the very popular EM method, although the former also performs poorly in animal model implementations. In that regard, few options to inference based on MCMC currently exist. Nevertheless, MCMC schemes based on Metropolis-Hastings sampling will allow a richer class of genetic models to be investigated. The GLMM inference in animal breeding is further aided by treating herds as random to allow a potentially greater use of data information. Finally, multiple-trait GLMM and censored genetic models should be used whenever the circumstances allow; however, further methodological developments are needed.

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