# Extending Generalized Linear Models with Random Effects and Components of Dispersion

Gegeneraliseerde Lineaire Modellen met Extra Stochastische Termen en Bijbehorende Variantiecomponenten

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# Extending Generalized Linear Models with Random Effects and Components of Dispersion

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## Stellingen

1. Het is nog steeds mogelijk met reeds lang bestaande modellen en technieken tot grote besparing van onderzoekskosten te komen. Zo kunnen met een combinatie van lineaire regressie en "double sampling" bij de voorspelling van het vleespercentage van varkenskarkassen de experimentele kosten worden gehalveerd, zonder verlies van nauwkeurigheid van de schattingen van de regressieco ëfficiënten.

   Engel, B., Walstra, P. (1991). Increasing precision or reducing expense in regression experiments by using information from a concomitant variable. *Biometrics* **47**, 13-20.

   Engel, B., Walstra, P. (1991). A simple method to increase precision or reduce expense in regression experiments to predict the proportion of lean meat of carcasses. *Animal Production* **53**, 353-359.

2. Het gebruik van een drempelmodel waarin een onderliggende variabele een "animal model" volgt, en analyse van de data volgens de methoden beschreven in Hoofdstuk 7 van dit proefschrift, leiden tot een efficiency verhoging met betrekking tot de genetische vooruitgang van 1 a 2 % ten opzichte van analyse met een conventioneel animal model voor normaal verdeelde data. Dit is slechts een kleine winst, maar wanneer de beste stieren selectief worden ingezet op de beste bedrijven, stijgt de winst tot 7 tot 20 %. Daarmee is aangetoond dat gebruik van het statistisch veel verantwoorder drempelmodel, ook voor grote data sets en voor resultaten op populatieniveau, in alle opzichten aantrekkelijk is.

   Meuwissen, T.H.E., Engel, B., van der Werf, J.H.J. (1995). Maximizing selection efficiency for categorical traits. *Journal of Animal Science* **73**, 1933-1939.

3. De Gibbs sampler produceert resultaten waar andere statistische technieken vanwege numerieke beperkingen falen. Onderzoekers omarmen tegelijk met dit algorithme schijnbaar probleemloos de bijbehorende Bayesiaanse filosofie. Binnen het statistiek onderwijs dient het onderscheid tussen frequentistische en Bayesiaanse beschouwingen scherper naar voren te worden gebracht opdat een meer bewuste keuze kan worden gemaakt.

4. Het gebruik van vertrouwde technieken, waar zij strikt genomen niet van toepassing zijn (denk aan variantieanalyse op discrete data), wordt vaak gerechtvaardigd met de opmerking dat "het meestal toch niet veel uitmaakt". Dit is de dood in de pot voor de ontwikkeling van nieuwe statistische modellen, die genuanceerdere conclusies toelaten.

5. Random effecten kunnen een veel grotere rol binnen de toegepaste statistiek spelen dan thans het geval is. Random effecten maken het mogelijk om grote aantallen parameters op stabiele wijze in een model op te nemen. Gelijkenis tussen experimentele eenheden kan worden weergegeven met behulp van een beperkt aantal variantiecomponenten.

6. De benaming "improper" voor niet-informatieve a priori verdelingen kan met recht met "onfatsoenlijk" vertaald worden: hier worden de regels van het probabilistisch fatsoen ruimschoots overschreden.

7. Een statisticus is niet objectief. Maar een goede statisticus probeert het, altijd weer opnieuw, wel te zijn.

8. Elk model is een karikatuur van de werkelijkheid. De grove lijnen zijn aanwezig, maar de details ontbreken. Er is geen enkele garantie dat de conclusies ontleend aan berekeningen binnen het model, relevant zijn voor de werkelijkheid. De enige rechtvaardiging is het succes bij gebruik voor praktijkproblemen. Daar er vaak geen alternatieven voor handen zijn, anders dan het blind nemen van besluiten, is succes al gauw verzekerd. Dit noopt op zijn minst tot bescheidenheid en voorzichtigheid.

9. Geld speelt geen rol zou heer Olivier B. Bommel zeggen. Dat geldt helaas niet voor de verzamelaars van het werk van Marten Toonder. Mede als gevolg van de adviesprijzen in de Bommelbibliografie van H. Matla (uitgeverij en antiquariaat Panda, Den Haag) liegen de prijzen voor bommeldingen er niet om. De Marten Toonder Verzamelaars Club zou zich de nobele taak moeten stellen om dit opgeschroefde prijsniveau te doorbreken: betaalbare facsimile uitgaves in eigen beheer zouden het vroege werk van Toonder weer binnen bereik van de oplettende lezertjes brengen.

10. Zeker in een tijd waar kinderen op school steeds meer moeten leren, mag vereenvoudiging van de spelling niet langer een punt van discussie zijn. De taal is in de eerste plaats een communicatiemiddel. Historische en culturele argumenten zijn hieraan ondergeschikt.

11. De thans nog experimentele wachttijdindicator bij stoplichten voor fietsers dient groot genoeg te zijn om in het voorbijgaan te kunnen worden afgelezen.

12. De wetenschap gaat aan management ten onder.

13. "De uitvreter" (de Gids, 1911) en "Titaantjes" (Groot Nederland, 1915) van Nescio (pseudoniem van J.H.F. Grönloh, 1881-1961) behoren tot de mooiste literatuur die in de Nederlandse taal is voortgebracht.

Stellingen behorende bij het proefschrift "Extending generalized linear models with random effects and components of dispersion" door Bas Engel, te verdedigen op 24 januari 1997 te Wageningen.

Voor Ineke

"Jelui kerels zijn zo akelig wijs: alles moet een reden en een doel hebben."

Nescio (J.H.F.Grönloh, 1881-1961), in "De uitvreter" (de Gids, 1911).

# Voorwoord

Dit proefschrift is een bundeling van artikelen over gemengde modellen, met name voor discrete data. Deze artikelen zijn het resultaat van onderzoek verricht binnen het onderzoeksprogramma van de Groep Landbouwwiskunde (GLW-DLO) ten behoeve van de onderzoeksinstituten binnen de Dienst Landbouwkundig Onderzoek (DLO) van het Ministerie van Landbouw, Natuurbeheer en Visserij.

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Willem Buist van het Instituut voor Veehouderij en Diergezondheid (ID-DLO) te Lelystad ben ik veel dank verschuldigd voor zijn bijdrage aan de verschillende simulatiestudies in dit proefschrift.

De werkgroep Gegeneraliseerde Lineaire Gemengde Modellen (Marijtje van Duijn (RU, Groningen), Jan Engel (CQM, Eindhoven), Janneke Hoekstra (RIVM, Bilthoven), Hans Jansen (CPRO-DLO, Wageningen), Bertus Keen (GLW-DLO, Wageningen) en Dick Wixley (Solvay Duphar, Weesp)) vormde gedurende enkele jaren een welkom klankbord.

Mijn promotoren Dieter Rasch en Hans van Houwelingen dank ik voor het vertrouwen om met mij in zee te gaan. Ook de overige leden van de promotiecommissie wil ik bedanken voor hun bereidheid om zich over mijn verzamelde statistische pennevruchten te buigen.

Wanneer ik aan een artikel werk, word ik er op bepaalde momenten niet gezelliger van voor mijn omgeving. Ineke, Jasper en Josien bied ik daarom, niet voor de eerste keer, mijn excuses aan voor al die momenten waarop ik, ondanks alle goede voornemens, toch met een hoofd vol gegeneraliseerde lineaire mixed modellen rondliep.

Contents

# Chapter 1

## Introduction

Introduction to generalized linear mixed models. Problems with evaluation of the likelihood. Introduction to estimation by iterative re-weighted restricted maximum likelihood. An outline of this dissertation.

# 1. Introduction

For analysis of independent normal data there is the linear model, e.g. analysis of variance or linear regression. For analysis of non-normal data there are generalized linear models (GLMs) (McCullagh and Nelder, 1989), e.g. logistic regression for binary and binomial variables or log-linear models for Poisson data. For analysis of dependent normal data there are linear mixed models (LMMs) (Searle, Casella and McCulloch, 1992), e.g. the split-plot model. But, for analysis of dependent non-normal data, for a long time, little was available, except for some particular problems.

Anderson and Hinde (1988) extended the framework of GLMs to more than one error structure to model dependent data. They concentrated on a fitting procedure which combines an EM algorithm with numerical integration to obtain maximum likelihood estimates for the parameters in the model. We will refer to the new class of models as generalized linear mixed models (GLMMs). Maximum likelihood in GLMMs has been considered by a number of authors, see Jansen (1993) and references therein. The random effects introduced in the extra error structures have to be "integrated out" to obtain the likelihood of the data. In contrast with an ordinary LMM, in general this can not be done analytically. Numerical integration can be employed for models with one or two nested sets of random effects, but numerical problems with more ambitious designs, e.g. crossed random effects, are insurmountable.

In this dissertation an alternative for maximum likelihood estimation in GLMMs is studied that avoids high dimensional integration. This estimation procedure is referred to as iterative re-weighted restricted maximum likelihood (IRREML). Numerical restrictions are the same as for LMMs for normal data. IRREML can be implemented with existing software developed for LMMs. In this dissertation, facilities which are offered in the statistical language Genstat 5 (1993) are used. An outline of this dissertation is presented in Section 7. The sections in between offer a (hopefully) gentle introduction to the aforementioned LMM, GLM, GLMM and IRREML.

# 2 LMMs

To account for dependence between observations, the linear model can be extended with extra random effects. Observations $y_1$ and $y_2$, which have one or more of these random effects in common, are (positively) correlated, e.g.:

$$y_1 = \mathbf{x}_1'\boldsymbol{\beta} + u + e_1,$$
$$y_2 = \mathbf{x}_2'\boldsymbol{\beta} + u + e_2.$$

Here, u is a common random effect and $e_1$ and $e_2$ are residual error terms. Elements of the vector of unknown parameters $\boldsymbol{\beta}$ are referred to as *fixed effects*. $\mathbf{x}_1$ and $\mathbf{x}_2$ are known design

vectors. Assuming independence between u, $e_1$ and $e_2$, the correlation between the two observations is:

$$\rho = \sigma_1^2 / (\sigma_1^2 + \sigma_0^2),$$

where $\sigma_1^2$ is the variance of u and $\sigma_0^2$ is the residual variance. Usually, normality is assumed:

$$u \sim N(0, \sigma_1^2) \quad \text{and} \quad e \sim N(0, \sigma_0^2).$$

Extension towards c sets of random effects with *variance components* $\sigma_1^2$ ... $\sigma_c^2$ is straightforward.

Although observations may be dependent, two of the key-properties of the linear model still hold:

(1) the mean $\mu$ of an observation y is a linear function of the unknown parameters in vector $\boldsymbol{\beta}$: $\mu = \mathbf{x}'\boldsymbol{\beta}$, and

(2) variances and covariances are functionally independent of the mean, e.g.: $\text{Var}(y) = \sigma_1^2 + \sigma_0^2$ and $\text{Cov}(y_1,y_2) = \sigma_1^2$ or 0 (the value of the covariance depending on whether observations have a common random effect).

## 3. GLMs

For non-normal variables, (1) and (2) are often unrealistic and undesirable. For example, for binary observations (y = 0 or 1), the mean $\mu$ is a probability between 0 and 1, leading to difficulties with respect to (1) (unless $\mu$ is confined to a narrow range), while the variance depends on the mean: $\text{Var}(y) = \mu(1-\mu)$, which clashes with (2) (again, unless $\mu$ is confined to a narrow range).

In a GLM, means $\mu$ are non-linear functions of parameters in $\boldsymbol{\beta}$. All the non-linearity is concentrated in the known *link function* g(.):

$$g(\mu) = \eta = \mathbf{x}'\boldsymbol{\beta}, \text{ or}$$
$$\mu = G(\eta) = G(\mathbf{x}'\boldsymbol{\beta}),$$

where G(.) is the inverse of g(.) and $\eta = \mathbf{x}'\boldsymbol{\beta}$ is referred to as the *linear predictor*. For binary data, a popular link function is the logit, which "stretches" the interval (0, 1) into $(-\infty, +\infty)$:

$$\text{logit}(\mu) = \log(\mu/(1-\mu)) = \eta = \mathbf{x}'\boldsymbol{\beta}.$$

Familiar concepts from analysis of variance and linear regression, such as interaction between experimental factors, or linear and quadratic terms of an explanatory variable, which

make little sense on the original scale, can be usefully employed on the link scale. Furthermore, variances may depend on the mean through a known *variance function* V(.):

$$\mathrm{Var}(y) = V(\mu).$$

For example, for binary data: $V(\mu) = \mu(1-\mu)$. Although (1) and (2) are now considerably relaxed, in GLMs correlated observations are not allowed, in contrast to LMMs.

## 4. GLMMs

Clearly, for some applications a combination of features from LMMs and GLMs may be needed in modelling the data, e.g. to analyse dependent binary data. An obvious and direct way to do so is to introduce additional random effects in the linear predictor $\eta$:

$$\eta = \mathbf{x}'\boldsymbol{\beta} + \mathbf{z}'\mathbf{u}.$$

Here, the random effects are collected in a vector $\mathbf{u}$ and $\mathbf{z}$ is a design vector corresponding to observation y. For example, for two correlated binary variables with a common random effect u:

$$\begin{aligned}
&E(y_1 \mid u) = \mu_1,\ E(y_2 \mid u) = \mu_2,\\
&\mathrm{Var}(y_1 \mid u) = V(\mu_1) = \mu_1(1-\mu_1),\ \mathrm{Var}(y_2 \mid u) = V(\mu_2) = \mu_2(1-\mu_2),\\
&\mathrm{logit}(\mu_1) = \eta_1 = \mathbf{x}_1'\boldsymbol{\beta} + u,\ \mathrm{logit}(\mu_2) = \eta_2 = \mathbf{x}_2'\boldsymbol{\beta} + u,\\
&u \sim N(0, \sigma_1^2).
\end{aligned}$$

This is an example of a generalized linear mixed model (GLMM).

## 5. Maximum likelihood estimation in GLMMs

The main topic of this dissertation is inference on parameters $\boldsymbol{\beta}$ and $\sigma_1^2 \ldots \sigma_c^2$ in GLMMs and we will briefly discuss why this is a problem which deserves special attention.

In GLMs parameters are estimated by maximum likelihood (ML). In LMMs parameters are estimated by a combination of ML and restricted (or residual) maximum likelihood (REML). REML (Patterson and Thompson, 1971) is a modified ML procedure for estimation of the components of variance $\sigma_1^2 \ldots \sigma_c^2$. ML estimators of components of variance may be severely biased when the number of elements of $\boldsymbol{\beta}$ is relatively large. The likelihood which is maximized with REML is not the likelihood of the observations collected in the vector y, but of contrasts $\mathbf{a}'\mathbf{y}$ with $E(\mathbf{a}'\mathbf{y}) = 0$. That is, before the components of variance are estimated, the fixed effects are "removed" by replacing the observations by a complete set

of "residuals" $\mathbf{a}'\mathbf{y}$. This may reduce the bias of the variance component estimators considerably. Elements of $\boldsymbol{\beta}$ are estimated by ML, as if the components were known and equal to their REML estimates.

Ignoring, for the moment, the REML modification, consider ML estimation of parameters in a GLMM. Suppose that $k(\mathbf{u})$ is the (normal) probability density function (pdf) of random effects $\mathbf{u}$ and $f(\mathbf{y} \mid \mathbf{u})$ is the pdf of $\mathbf{y}$ conditional upon $\mathbf{u}$. The likelihood l is equal to:

$$l = \int \ldots \int f(\mathbf{y} \mid \mathbf{u})\, k(\mathbf{u})\, d\mathbf{u},$$

and involves evaluation of a generally high dimensional integral. When both $f(. \mid .)$ and $k(.)$ are pdf's of normal distributions, integration is straightforward. But, when $(\mathbf{y} \mid \mathbf{u})$ follows a non-normal distribution, in most applications, no tractable analytical form is available for the likelihood. This means that, still accepting ML estimation as the proper starting point, some form of approximation is required.

One way to proceed is to make judicious choices for $f(. \mid .)$ and $k(.)$ such that the integral can be analytically evaluated. This may be fine for some applications with fairly simple correlation structures of two or three nested sets of random effects, see for instance van Duijn (1993), and even there considerable mathematical ingenuity is required, but it does not generalize to more complicated models.

Another possibility is to replace integration by summation. An example is Gauss-Hermite quadrature, where :

$$l \approx \Sigma\, w_i\, f(\mathbf{y} \mid a_i).$$

For principles behind the choice of points $a_1 \ldots a_m$ and weights $w_1 \ldots w_m$, which are extensively tabled, see e.g. Dahlquist, Björck and Anderson (1974, §7.4.6) and Abramowitz and Stegun (1965, p924). In principle we can approximate the integral as close as we like, simply by choosing m large enough. However, although this may be a useful approach for models with one or two nested sets of random effects, where elegant algorithms have been developed, see for instance Jansen (1993), the computational burden quickly becomes insuperable for more ambitious designs, e.g. two crossed random factors. So, clearly with respect to ML estimation we do have a problem.

## 6. IRREML

Initially, in Engel and Keen (1994) we did not consider ML as a starting point, but concentrated on extension of iterative re-weighted least squares (IRLS), which is a general algorithm for estimation in GLMs, see for instance McCullagh and Nelder (1989, §2.5). This algorithm is based on linearization of the mean $\mu$ around initial (current) values $\boldsymbol{\beta}_0$ for $\boldsymbol{\beta}$:

$\mu \approx \mu_o + [d\mu/d\eta]_{\beta_o}[d\eta/d\boldsymbol{\beta}]_{\beta_o}'(\boldsymbol{\beta}-\boldsymbol{\beta}_o) = \mu_o + g'(\mu_o)^{-1}\,\mathbf{x}'(\boldsymbol{\beta}-\boldsymbol{\beta}_o)$, from which
$\mathbf{x}'\boldsymbol{\beta} \approx \mathbf{x}'\boldsymbol{\beta}_o + g'(\mu_o)(\mu-\mu_o)$,

where $g'(.)$ is the derivative of $g(.)$. This implies that the following artificial dependent variable $\zeta$, which will be referred to as the *adjusted dependent variate*, approximately follows a linear model:

$$\zeta = \mathbf{x}'\boldsymbol{\beta}_o + g'(\mu_o)(y-\mu_o),$$

with

$$E(\zeta) \approx \mathbf{x}'\boldsymbol{\beta} \text{ and } Var(\zeta) \approx g'(\mu_o)^2\, V(\mu_o).$$

Parameters can be estimated by iterative use of weighted regression on $\zeta$ with *iterative weights* $w = \{g'(\mu_o)^2\, V(\mu_o)\}^{-1}$. In a GLM this is equivalent to Fisher scoring and the final estimates are ML estimates.

In a GLMM, the same adjusted dependent variate $\zeta$ may be considered. This variate approximately follows a LMM and iterated weighted least squares may be replaced by iterated weighted REML, employing the same iterative weights as before. Inference based on this estimation procedure, which will be referred to as iterative re-weighted REML (IRREML), is the principal subject of this dissertation. In addition to being a straightforward extension of IRLS, IRREML has the added advantage that it can be implemented with the facilities for fitting LMMs in Genstat 5 (1993). As a bonus, methodology developed for inference in LMMs is potentially useful for GLMMs, when applied to the adjusted dependent variate $\zeta$ from the last iteration step.

Although, as shown in Chapter 11, IRREML can be presented as an approximation to ML, it has merit of its own as well. Notably, there is no need for full specification of the distribution of $\mathbf{y}$ conditional upon $\mathbf{u}$. It suffices to specify the first two conditional moments of $(\mathbf{y} \mid \mathbf{u})$. This is a feature which IRREML shares with maximum quasi-likelihood estimation (see e.g. McCullagh and Nelder, 1990, Ch.9). Although maximum quasi-likelihood estimation is less efficient than ML estimation, it may be considerably more robust with respect to distributional assumptions. The same can be expected of IRREML versus ML estimation.

## 7. An outline of this dissertation

Since many inferential aspects of REML for ordinary LMMs carry over to the approximate LMM for the adjusted dependent variate $\zeta$ in IRREML, an overview of REML for LMMs is presented in Chapter 2.

IRREML has a lot in common with maximum quasi-likelihood estimation. Therefore, maximum quasi-likelihood estimation is the subject of Chapter 3.

IRREML is introduced in Chapter 4. The method has been proposed independently by a number of authors, as an extension of IRLS (Schall, 1991; Engel and Keen, 1994), or as an approximation of ML estimation employing Laplacian integration (Breslow and Clayton, 1993; Wolfinger, 1993; Wolfinger and O'Connell, 1993), or motivated by Bayesian arguments (McGilchrist, 1994).

A first attempt by simulation to increase confidence in estimation by IRREML is presented in Chapter 5. A practical problem, involving carcass classification of cattle, is analysed with IRREML. The data are fractions $y = x / n$ and the link function is the logit link. The variance function is assumed to be the same as for the binomial distribution, but an unknown multiplicative over-dispersion parameter $\phi$ is included in the conditional variance:

$$\mathrm{Var}(y \mid \mathbf{u}) = \phi\, V(\mu) = \phi\, \mu(1-\mu) / n.$$

In the approximate LMM, parameter $\phi$ is casted for the role of "residual variance" and estimated from the data together with the other components of variance. The distribution of $(\mathbf{y} \mid \mathbf{u})$ remains unspecified. The final model fitted to the classification data includes four components of variance additional to the multiplicative over-dispersion factor. This extensive data set, which is very unbalanced, is used as a basis for a simulation study. Simulation results are presented for IRREML and for LMM procedures applied to $\zeta$ in the last iteration step. This includes a study of procedures for constructing confidence intervals and significance tests for fixed effects and components of variance. IRREML and the modified LMM procedures are seen to perform quite satisfactorily.

Threshold models for binary data are a sub-class of the class of GLMMs. In Chapter 6, estimation by IRREML in threshold models is studied, where IRREML is found to perform poorly when the number of binary observations per random effect is small. The bias for components of variance may be considerable. It is found that, in contrast to results in the literature, both under- and over-estimation may occur, depending on the number of fixed effects in the model.

In Chapter 7, IRREML is extended towards threshold models for ordinal data, e.g. scores 1, 2, 3 or 4 with score 1 for "no damage" to score 4 for "severe damage". These models may include both fixed and random effects with associated components of variance on the underlying scale. The residual error distribution on the underlying scale is rendered more flexible by introducing additional shape parameters, e.g. a kurtosis parameter or parameters to model heterogeneous residual variances as a function of factors and covariates. The threshold values, and the additional shape parameters, are regarded as parameters in the link function. They are estimated by linearizing $\mu$ with respect to $\boldsymbol{\beta}$, $\mathbf{u}$ ánd the threshold values and additional shape parameters.

In Chapter 8, we return to the threshold model for binary data. The simulation study of Chapter 6 is extended and two methods to reduce bias of variance component estimators, one proposed by Breslow and Lin (1995) and the other by Engel, Buist and Visscher (1995),

are studied. Minimal dimensions for the data are identified, such that bias and root mean squared error of intra-class correlation or heritability estimators are of modest size and useful inference is feasible.

In Chapter 9, we return to normal data. Here it is shown how the ideas behind IRREML can be applied to a mixed model with heterogeneous variances. Means and variances in this model are expressed in terms of fixed and random effects, involving both additive and multiplicative effects. The model was developed as a basis for a new national breeding evaluation method for Dutch dairy cattle and the estimation procedure was implemented by the Dutch Cattle Syndicate in 1995. Datasets in the dairy industry are extremely large, and therefore computational aspects are very important. With the estimation procedure developed for the new breeding evaluation system, a data set comprising 12,629,403 observations on 5,819,606 cows from 42,480 herds collected over a period of 16 years is analysed.

Finally, in Chapter 10, the relationship between IRREML and ML, which is already indicated in some of the preceding chapters, is discussed in more detail. This chapter is based on a contribution (Engel and Keen, 1996) to the discussion of a paper by Lee and Nelder (1996). Here, a central role is given to Laplace integration (see e.g. Wolfinger, 1993), where the logarithm of the joint pdf of $\mathbf{y}$ and $\mathbf{u}$: $h(\mathbf{y},\mathbf{u}) = \log(f(\mathbf{y} \mid \mathbf{u})) + \log(k(\mathbf{u}))$ under the integral in the likelihood is approximated. Writing the likelihood in the form:

$$l = \int \ldots \int \exp(h(\mathbf{y},\mathbf{u}))\, d\mathbf{u},$$

$h(\mathbf{y},\mathbf{u})$ is approximated by a quadratic in $\mathbf{u}$ around the value $\hat{\mathbf{u}}$ where $[\partial h(\mathbf{y},\mathbf{u})/\partial \mathbf{u}]_{\hat{\mathbf{u}}} = \mathbf{0}$. Now, the integral can be evaluated, similar to the case of two normal pdf's. The result is basically a single point version of Gauss-Hermite quadrature and can be used to motivate IRREML as an approximate ML method.

## 8. The future

In a Bayesian context, Gibbs sampling has been proposed for inference in GLMMs (Zeger and Karim, 1991; Karim and Zeger, 1992). Gibbs sampling is a technique to sample from a posterior distribution. Its computational demands are much higher than for IRREML. Problems and pitfalls such as choice of length of the Gibbs chain, convergence and choice of (non-informative) prior distributions are illustrated in Zeger and Karim (1991). Occasionally results obtained with the Gibbs sampler are interpreted in a frequentistic way. Although conceptually a bit awkward, this allows us to compare results of Gibbs sampling and IRREML on an equal footing. For instance with respect to bias and mean square error of point estimates, when in case of Gibbs sampling posterior means, modes or medians are used. In this light, the Gibbs sampler may be regarded as a powerful numerical integration technique and is a serious competitor for IRREML. An important point is whether for

practical sample sizes a substantial reduction in bias or root mean squared error can be obtained with the Gibbs sampler, and to what extent this is at the cost of robustness with respect to distributional assumptions.

There is obviously still a lot to be done in the area of unbalanced mixed models, both for normal and non-normal data. Inference on fixed effects still does not properly account for estimation of the components of variance. Or in other words, for unbalanced data, there are no F-tests for (subsets of) fixed effects. Little is known with respect to general guidelines for inference in the form of significance tests and confidence intervals for components of variance. This dissertation addresses inference *after* the data have been collected. All examples are from observational studies. In observational studies the structure of the data and that of the model employed for the analysis are often complicated. General guidelines with respect to design are difficult to give, although to my experience, simulation of complicated models for a variety of parameter configurations, including random elements in the design, can be very useful. For controlled experiments, in an industrial context for instance, "balance" in the data enables the use of particular models and estimation procedures, see e.g. Engel (1987). In that case derivation of analytical results with respect to efficiency of the design may be feasible and is of obvious importance.

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# Chapter 2

## The analysis of unbalanced linear models with variance components

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An overview of inferential techniques for normal data mixed models. Many of the concepts discussed will re-appear in later chapters about mixed models for non-normal data.

# The analysis of unbalanced linear models with variance components

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Statistical inference for fixed effects, random effects and components of variance in an unbalanced linear model with variance components will be discussed. Variance components will be estimated by Restricted Maximum Likelihood. Iterative procedures for computing the estimates, such as Fisher scoring and the EM-algorithm, are described.

*Key Words & Phrases:* variance component estimation, analysis of variance, mixed model, REML, Fisher scoring, EM-algorithm.

## 1. Introduction

In a variance component model for a balanced layout, under Normality, exact and efficient tests and procedures for constructing confidence intervals for location parameters (fixed effects) are available. Estimates of location parameters are simple linear combinations of observations. Estimates of dispersion parameters (components of variance) may be obtained by the ANOVA method from the sums of squares corresponding to the different sources of random variation (random effects) in the model (Searle, 1971, 1987). ANOVA estimates may be negative. This can be a complication, especially in comparatively small experiments where the probability for a negative estimate can be sizeable, see Verdooren (1982). However, generally the analysis of a balanced layout is fairly straightforward. For an elegant theoretical framework in terms of linear spaces see Verdooren (1969).

In an unbalanced layout the analysis is usually far from straightforward. Most of the properties which hold for a balanced layout, such as sums of squares following independent (non-central) chi-square distributions under Normality, are lost. Only for particular models some exact results for statistical inference are still available. Many procedures for estimation of variance components have been suggested in the literature. Luckily only a handful have survived the ravages of time: Henderson's method III (the fitting constants method) (Searle, 1971, 1987), Maximum Likelihood (ML), Restricted (or Residual) Maximum Likelihood (REML) (Patterson and Thompson, 1971), Minimum Norm Quadratic Unbiased Estimation (MINQUE) (Rao, 1971) and

Minimum Variance Quadratic Unbiased Estimation (MIVQUE) (LAMOTTE, 1973). For all these estimation procedures the calculations involved may be considerable.

Harvey's LSML76 program (HARVEY, 1970, 1977) has given a big boost to the use of Henderson's method III. Henderson III is an oldtimer, still going strong, but slowly clearing the field for its younger competitors, probably because it has not much to vouch for, apart from conceptual simplicity. In general Henderson III does not offer unique estimates (SEARLE, 1971, 1987). Estimators are unbiased, but only when values outside the parameter space are allowed. When negative values are replaced by zero the estimators will have a positive bias.

MINQUE and MIVQUE estimates may be negative and replacing negative estimates by zero will result in a positive bias. Both MINQUE and MIVQUE start from a priori values for the components of variance. For an unbalanced layout the estimates will depend on the a priori values. MINQUE with the Euclidean norm and MIVQUE under Normality (with any other distribution MIVQUE is just a mess), starting from the same a priori values, will produce the same estimates. Repeatedly using the estimates as a priori values for a next step of MINQUE or MIVQUE has intuitive appeal and removes the dependence on the a priori values. When, after convergence, positive estimates are obtained with iterated MINQUE (with the Euclidean norm) or iterated MIVQUE (under Normality), REML will produce the same estimates.

REML is a (modified) maximum likelihood procedure. By definition ML and REML estimators are non-negative. ML estimators may have a sizeable bias, particularly when the number of fixed effects in the model is large relative to the number of observations. REML estimators usually have a much smaller bias, possibly, but certainly not always, at the cost of an increase in mean squared error.

For a balanced layout the ANOVA estimates, when they are positive, will agree with the estimates from Henderson III, MINQUE, MIVQUE and REML.

Simulation studies and analytical comparisons, see KLOTZ et al. (1969), HOCKING and KUTNER (1975), CORBEIL and SEARLE (1976b)[1], SAHAI (1976)[1], HARVILLE (1978)[1], LI and KLOTZ (1978), SWALLOW and SEARLE (1978), MILLER (1979), QUAAS and BOLGIANO (1979), LIN and MCALLISTER (1983), SWALLOW and MONAHAN (1984) and LEE and KAPADIA (1984, 1989), do not indicate a clear-cut winner among the five methods with respect to bias and mean-square-error. REML is a reasonable compromise in view of its coherence with the other methods.

This paper will concentrate on REML. However, after some modification, much of the contents of this paper will hold for Henderson III, MINQUE,

1) Non-negativity of maximum likelihood estimators is not taken into account in CORBEIL and SEARLE (1976b) and HARVILLE (1978), see LEE and KAPADIA (1984). SAHAI (1976) contains an error, see LI and KLOTZ (1978).

MIVQUE and ML as well. In sections 2 and 3 the mixed model and REML will be introduced. Section 4 deals with statistical inference for fixed effects, random effects and components of variance. Sections 5 and 6 will concern derivatives of the log likelihood of REML and an outline of iteration schemes such as Fisher scoring and the EM-algorithm. In the calculations storage and inversion of large matrices must be avoided and numerical strategies to serve that end are discussed in section 7.

New methods for estimation of variance components still crop up, often motivated by a need for numerical simplification in the analysis of large data sets, see for instance SCHAEFFER (1986, 1987). For a historical review of variance component estimation see ANDERSON (1979) and FREEMAN (1979). Bibliographies may be found in SAHAI (1979) and SAHAI and KHURI (1985a,b).

Many details on the contents of this paper may be found in HARVILLE (1977), SEARLE (1979), HENDERSON (1986a) and ENGEL (1989) (available from the author).

## 2. THE MODEL AND SOME NOTATION

### *2.1. The model*

In the variance components model a vector $y$, consisting of $n$ observations, can be written as:

$$y = X\alpha + Z_1 b_1 + Z_2 b_2 + \ldots + Z_c b_c + e, \tag{1}$$

where $X$ is a known $n \times p$ matrix, $\alpha$ a $p \times 1$ vector of unknown constants, $Z_i$ a known $n \times q_i$ matrix, $b_i$ a $q_i \times 1$ vector of unknown random variables and $e$ a $n \times 1$ vector of unknown random variables.

It is assumed that $b_1 \ldots b_c, e$ are independently Normally distributed:

$$\begin{aligned} b_i &\sim N(0, A_i \sigma_i^2) \\ e &\sim N(0, R\sigma_0^2), \end{aligned} \tag{2}$$

where $A_i$ and $R$ are known positive definite matrices and $\sigma_0^2, \sigma_1^2, \ldots, \sigma_c^2$ are unknown non-negative constants.

The vector $\alpha$ represents the fixed effects in the model, $b_1 \ldots b_c$ are the random effects, $e$ is a vector of residual error terms and $\sigma_0^2 \ldots \sigma_c^2$ are the components of variance.

It is assumed that $X$ is of full column rank, i.e.

$$\text{rank}(X) = p. \tag{3}$$

This assumption can always be satisfied by a suitable reparameterization.

Which of the ingredients in the model are of interest will depend on the particular problem at hand:

- Some of the elements of $\alpha$, representing treatment contrasts, may be of interest, while $b_1 \ldots b_c$ are introduced to take account of correlations between the observations. For example the random effects may represent

a block/plot/subplot . . . structure in a field experiment.

- In animal breeding research random effects may represent genetic contributions from parents to their offspring (for instance with respect to milk production of cows). The components of variance will indicate to what extent the genetic background of an animal is of importance and what is to be gained by selection among the parents. Often $\alpha$ will represent differences between herds, years and seasons, (HYS-effects), which in this context are nuisance parameters. The components of variance are of prime interest to determine the heritability and selection response. In a selection experiment selection will be based on predictions for the relevant random effects.
- In a production system various sources of random variation may be quantified by components of variance in a mixed model, indicating possibilities for improvement. A similar example is an inter-laboratory experiment where differences between batches of the same material, between laboratories and between analysts within laboratories are some of the different sources of variation. From the components of variance measures such as reproducibility and repeatability may be derived. For more examples see ROBINSON (1987b).

Even when fixed effects are of prime interest, predictions for the random effects and residuals may be used to check for departures from model assumptions and outliers. The relative sizes of the variance components may suggest more efficient designs for future experiments.

*2.2 Notation*

Matrices $Z_1,...Z_c$ and vectors $b_1...b_c$ may be collected in a matrix $Z=(Z_1...Z_c)$ and vector $b=(b_1'...b_c')'$. $Z$ is a $n\times q$ matrix and $b$ a $q\times 1$ vector where $q$ is the total number of levels of the random effects, i.e. $q=\Sigma q_i$. Sometimes it will be convenient to collect the components of variance in a $(c+1)\times 1$ vector: $\sigma^2=(\sigma_0^2,\sigma_1^2,...,\sigma_c^2)'$. The following ratios will be useful:

$$\gamma_i=\sigma_i^2/\sigma_0^2 \text{ and } \lambda_i=\sigma_0^2/\sigma_i^2, \quad i=1...c. \tag{4}$$

The $q\times q$ variance-covariance matrix of vector $b$ scaled by the residual variance $\sigma_0^2$ is

$$D = \text{Var}(b)/\sigma_0^2 = \text{diag}(\gamma_i A_i). \tag{5}$$

The $n\times n$ variance-covariance matrix of the vector of observations $y$ is a highly structured matrix and a linear function of the components of variance:

$$V=\text{Var}(y)=\sigma_0^2 H, \text{ where } H=ZDZ'+R=\sum\gamma_i Z_i A_i Z_i'+R. \tag{6}$$

Finally the following matrices are important:

$$M=I-X(X'X)^{-1}X', \quad P=V^{-1}-V^{-1}X(X'V^{-1}X)^{-1}X'V^{-1}, \tag{7}$$
$$S=R^{-1}-R^{-1}X(X'R^{-1}X)^{-1}X'R^{-1}, \quad C=(Z'SZ+D^{-1})^{-1}.$$

$M$ is the projection matrix on the orthogonal complement of span($X$): the linear space spanned by the columns of $X$. $P$ is the Moore-Penrose generalised inverse of MVM. For a brief introduction to the Moore-Penrose inverse see LOWERRE (1982). In Bayesian context, with a vague prior for $\alpha$, $P$ is the inverse of the variance-covariance matrix of $y$. $S$ is the Moore-Penrose inverse of MRM. Matrix $C$ will be important for prediction of the vector of random effects $b$. The following properties will be useful:

$$H^{-1}=R^{-1}-R^{-1}Z(Z'R^{-1}Z+D^{-1})^{-1}Z'R^{-1} \tag{8}$$

$$PX=0,\ X'P=0,\ PVP=P$$

$$P=\{S-SZ(Z'SZ+D^{-1})^{-1}Z'S\}\ \sigma_0^{-2}=\{S-SZCZ'S\}\sigma_0^{-2}.$$

Expressions for $H^{-1}$ and $P$ follow from RAO (1973) (p. 33, exercise 2.9).

*2.3 A restriction*

In agreement with many applications the following simplifying restriction will be made in this paper (unless stated otherwise):

$$A_i=I_{q_i} \quad i=1...c \quad \text{and} \quad R=I_n. \tag{9}$$

Observe that any model satisfying (1) and (2) may be transformed to satisfy (9):

$$\tilde{y}=R^{-\frac{1}{2}}y,\ \tilde{X}=R^{-\frac{1}{2}}X,\ \tilde{Z}_i=R^{-\frac{1}{2}}Z_iA_i^{\frac{1}{2}},$$

$$\tilde{b}_i=A_i^{-\frac{1}{2}}b_i,\ \tilde{e}=R^{-\frac{1}{2}}e. \tag{10}$$

Notable exceptions to (9) occur in animal breeding. Genetic relationships between animals may be represented by $A_i \neq I_{q_i}$. For examples see HENDERSON (1976, 1986b, c) and QUAAS (1976). In multi-trait models for each animal a number of traits are observed. Such a model can be expressed in the form (1) with $A_i$ following from variances and covariances between traits and genetic relationships between animals, see HENDERSON (1986a, c). In section 7 we will look briefly at models which are relevant to animal breeding research with $A_i$ or $R$ unequal to the identity matrix. Observe that under (9)

$$S=M \tag{11}$$

$$P=\{M-MZ(Z'MZ+D^{-1})^{-1}Z'M\}\ \sigma_0^{-2}$$

$$=(M-MZCZ'M)\sigma_0^{-2},\ \text{with}\ C=(Z'MZ+D^{-1})^{-1}. \tag{12}$$

## 3. REML

### *3.1. Introduction*

Restricted Maximum Likelihood (PATTERSON and THOMPSON, 1971) is a maximum likelihood method, however it is not the likelihood of the vector of observations $y$ which is maximized, but the likelihood of a vector $Qy$, where $Q$ is any $(n-p)\times n$ matrix satisfying

$$\text{rank}(Q)=n-p \text{ and } QX=(0). \tag{13}$$

The log likelihood of $Qy$, under the assumption of Normality (2), is

$$L = -\tfrac{1}{2}(n-p)\log(2\pi)-\tfrac{1}{2}(n-p)\log(\sigma_0^2)-\tfrac{1}{2}\log(|QHQ'|)$$

$$-\tfrac{1}{2}y'Q'(QHQ')^{-1}Qy\sigma_0^{-2}. \tag{14}$$

It may be shown that

$$y'Q'(QHQ')^{-1}Qy\sigma_0^{-2}=y'Py,$$

$$|QHQ'|=|QQ'||D||Z'MZ+D^{-1}|.$$

Hence,

$$L=-\tfrac{1}{2}(n-p)\log(2\pi)-\tfrac{1}{2}(n-p)\log(\sigma_0^2)-\tfrac{1}{2}\log(|QQ'|)$$

$$-\tfrac{1}{2}\log(|D|)-\tfrac{1}{2}\log(|Z'MZ+D^{-1}|)-\tfrac{1}{2}y'Py. \tag{15}$$

Observe that although $Q$ is not uniquely determined by (13), the log likelihood $L$ is determined up to the unimportant constant $\log(|QQ'|)$ in (15).

### *3.2. Rationale*

For a random sample $y_1 \ldots y_n$ from a univariate Normal distribution with mean $\mu$ and variance $\sigma^2$ the ML estimator of $\sigma^2$ is $\Sigma(y_i-\bar{y})^2/n$. This estimator is biased downward: the ML estimator does not take into account the loss of one degree of freedom resulting from the estimation of $\mu$ by the mean $\bar{y}$. The REML estimator is obtained by replacing the divisor $n$ by $(n-1)$ and is unbiased.

In a mixed model the loss in degrees of freedom due to the fixed effects may be substantial, resulting in a sizeable bias for ML estimators. REML estimators generally yield a smaller bias, often, but not always, at the cost of a higher mean squared error.

With the transformation (VERDOOREN, 1980):

$$\tilde{y}=\begin{bmatrix} Q \\ X'H^{-1} \end{bmatrix} y$$

the log likelihood of $y$ may be written as $L+L_0$, where $L$ is the REML log likelihood from (14) and $L_0$ corresponds to $X'H^{-1}y$. $L$ represents the translation invariant part of the log likelihood: it does not depend on the fixed effects. Since ML estimators of $\alpha$ and $H$ are satisfying

$$\hat{\alpha}_{ML}=(X'\hat{H}_{ML}^{-1}X)^{-1}X'\hat{H}_{ML}^{-1}y, \tag{16}$$

the part of $L_0$ which depends on $y$ yields 0 after substitution of (16). Hence, the ML estimator for $\sigma^2$ also depends on $y$ through $Qy$ only. Both REML and ML are using the translation invariant information and there is no obvious loss of information by using REML instead of ML for estimation of $\sigma^2$.

REML may also be obtained by an EM-algorithm, see DEMPSTER et al. (1977, 1984): at the start of step $(t+1)$ of the algorithm let the components of variance be $\sigma^2_{i[t]}$. Independent prior distributions are assumed:

$$\alpha\sim N(0,I_p\tau^2),\ b_i\sim N(0,I_{q_i}\sigma^2_{i[t]}),\ e\sim N(0,I_n\sigma^2_{0[t]}).$$

Then:

$$\mathrm{Var}(y)=X'X\tau^2+V_{[t]} \text{ and } \lim_{\tau^2\to\infty}[\ \mathrm{Var}(y)]^{-1}=P_{[t]},$$

where $V_{[t]}$ and $P_{[t]}$ correspond to (6) and (7) with simplifications (9), (11) and (12). The limit $\tau^2\to\infty$ introduces a vague prior for the fixed effects. New values for the components of variance are obtained from:

$$\sigma^2_{i[t+1]}=E(b_i'b_i|y)/q_i,\quad \sigma^2_{0[t+1]}=E(e'e)|y)/n,$$

where the conditional expectations are evaluated for the old iterates $\sigma^2_{[t]}$. When the proces converges, the solution will correspond to a stationary point of the REML likelihood.

## 4. INFERENCE

### *4.1. Fixed effects and random effects*

Fixed effects may be estimated by generalized least squares:

$$\hat{\alpha}=(X'H^{-1}X)^{-1}X'H^{-1}y, \tag{17}$$

where $H$ is replaced by $\hat{H}$ obtained by replacing $\sigma_i^2$ by their REML estimates $\hat{\sigma}_i^2$. The resulting estimator $\hat{\alpha}$ is unbiased, provided that its expectation exists and is finite (KACKAR and HARVILLE, 1981). This also holds when $\sigma^2$ is estimated by Henderson III, MIVQUE, MINQUE (replacing negative estimates by zero or a small positive number) or ML.

Predictions for random effects may be obtained from the regression of $b$ on $y$:

$$\hat{b}=DZ'H^{-1}(y-X\alpha), \tag{18}$$

where $D$ and $H$ are replaced by $\hat{D}$ and $\hat{H}$ derived from the REML estimates $\hat{\sigma}_i^2$ and $\alpha$ is replaced by $\hat{\alpha}$ from (17).

The estimate $\hat{\alpha}$ and prediction $\hat{b}$ are satisfying the mixed model equations (MMEs) (HENDERSON, 1963):

$$\begin{bmatrix} X'X & X'Z \\ Z'X & Z'Z+D^{-1} \end{bmatrix} \begin{bmatrix} \alpha \\ b \end{bmatrix} = \begin{bmatrix} X'y \\ Z'y \end{bmatrix}. \tag{19}$$

Observe that replacing (17) and (18) by (19) yields a considerable numerical reduction: the matrix $H$ to be inverted in (17) and (18) is of size $n \times n$, while the coefficient matrix of (19) is of size $(p+q)\times(p+q)$. The equations (19) follow from (17) and (18) by using the expression for $H^{-1}$ in (8).

Inference on $\alpha$ is often based on a normal approximation of the distribution of $\hat{\alpha}$:

$$\hat{\alpha} \sim N(\alpha, (X'\hat{V}^{-1}X)^{-1}), \text{ approximately.} \tag{20}$$

The upper left-hand part of the inverse of the coefficient matrix of the MMEs in (19) multiplied by $\hat{\sigma}_0^2$ is equal to the approximate variance-covariance matrix in (20). The lower right-hand part multiplied by $\hat{\sigma}_0^2$ is an approximation for the mean squared error $E[(\hat{b}-b)'(\hat{b}-b)]$.

Predictions for the random effects are important for selection purposes in animal breeding. They are often referred to as Best Linear Unbiased Predictions (BLUP), see for instance THOMPSON (1979), GIANOLA and GOFFINET (1982), SEARLE (1985) and GIANOLA et al. (1986).

In (20) the additional variability due to the estimation of $V$ is not taken into account. For linear contrasts $\delta'\alpha$, GIESBRECHT and BURNS (1985) suggest replacing the Normal approximation for

$$(\delta'\hat{\alpha})/\sqrt{(\delta'(X'\hat{V}^{-1}X)^{-1}\delta)}, \tag{21}$$

under the hypothesis $\delta'\alpha=0$, by a Student distribution. The approximate number of degrees of freedom follows from a Satterthwaite approximation for the approximate variance under the square root in the denominator of (21). Simulation in GIESBRECHT and BURNS (1985) and experience with a GENSTAT program (ENGEL et al., 1986 and VAN DEN BOL, 1987) indicate that this approximation performs well. In KACKAR and HARVILLE (1984) the Normal approximation is retained, but the standard error in the denominator of (21) is increased. Simulation results indicate that this may be a poor approach (KACKAR and HARVILLE, 1984).

### *4.2. Components of variance*

The normal distribution with mean $\sigma^2$ and variance-covariance matrix (see section 5):

$$2[(\text{trace } (Z'_iPZ_j\ Z'_jPZ_i))]^{-1} \tag{22}$$

may be used as an approximation for the distribution of the REML estimator $\hat{\sigma}^2$. As far as I know there are no papers dealing with the asymptotics of REML directly. However, MILLER (1977) dealing with ML and BROWN (1976)

dealing with (iterated) MINQUE are closely related to the subject. See also RAO and KLEFFE (1988). Little is known about the small sample behaviour of this approximation, a modest simulation is reported in GIESBRECHT and BURNS (1985), which does not look too bad with respect to the asymptotic variance-covariance matrix (22).

For selected models, under the Normality assumption, some exact tests and procedures for constructing confidence intervals are available, see SEELY and EL-BASSIOUNI (1983), HARVILLE and FENECH (1985), KHURI and LITTELL (1987) and VERDOOREN (1988). Nesting is generally a favourable feature. Harville and Fenech discuss models with $c=1$, which includes the split-plot design as an important representative. Khuri and Littell deal with the unbalanced two-way random model with interaction. We will look briefly at models with $c=1$. A confidence interval for $\sigma_0^2$ may be derived from the residual sum of squares (RSS) for the model with $b$ taken to be fixed: RSS $\sim\sigma_0^2\chi^2_{n-r}$, where $r=\text{rank}\,(X,Z)$. A confidence interval for $\gamma_1=\sigma_1^2/\sigma_0^2$ from (4) may be obtained from:

$$\frac{(\sigma_0^2 y'Py-\text{RSS})/(r-p)}{\text{RSS}/(n-r)} \sim F_{r-p;n-r}, \tag{23}$$

an alternative expression, when $\sigma_1^2 \neq 0$, is

$$\frac{([\hat{e}'\hat{e}+\lambda_1\hat{b}'\hat{b}]-\text{RSS})/(r-p)}{\text{RSS}/(n-r)} \sim F_{r-p;n-r}, \tag{24}$$

where
$$\hat{e} = y-X\hat{\alpha}-Z\hat{b}, \tag{25}$$

with $\hat{\alpha}$ and $\hat{b}$ solutions of the MMEs in (19). The part between square brackets in (24) is similar to a residual sum of squares and may be written as the difference between the total sum of squares of the observations and the inner product of the right-hand side and the solutions of the MMEs:

$$\hat{e}'\hat{e}+\lambda_1\hat{b}'\hat{b}=y'y-(\hat{\alpha}',\hat{b}')\begin{bmatrix}X'y\\Z'y\end{bmatrix}.$$

For $\sigma_1^2=0$ (23) is equivalent to the traditional $F$-ratio (observe that $b$ random with $E(b)=0$ and $\sigma_1^2=0$ is equivalent with $b$ fixed and $b=0$).

In general ($c\geqslant 2$) the $F$-test from the corresponding fixed effects model or from a corresponding balanced layout will not be a valid test for the hypothesis $\sigma_i^2=0$, since: (i) for $\sigma_i^2=0$ the expectations of the nominator and denominator will not agree, (ii) nominator and denominator are not distributed as multiples of chi-square distributions, (iii) nominator and denominator are not independent. By some juggling with the sums of squares corresponding to the random effects and a Satterthwaite approximation, (i) and (ii) can often be overcome, but not (iii). Beware for the likelihood-ratio test for the hypothesis $\sigma_i^2=0$ in combination with a chi-square approximation, see MILLER (1977).

## 5. Derivatives of the REML log likelihood

The first and second order derivatives of the log likelihood $L$ from (14) are listed below. All derivatives depend on expressions of the form $A'PB$ where $A$ and $B$ are any two equal or different elements of the collection $y, Z_1 \ldots Z_c$, such as $y'Py, y'PZ_1, Z'_1PZ_2$. $A'PB$ is referred to as the $W$- transform of matrices $A$ and $B$. This is a modification (Corbeil and Searle, 1976a) of a transformation introduced by Hemmerle and Hartley (1973).

$$\frac{\partial L}{\partial \sigma_i^2} = -\frac{1}{2} \text{ trace } (Z'_iPZ_i) + \frac{1}{2}(y'PZ_iZ'_iPy), \quad i = 0, 1 \ldots c \tag{26}$$

$$\frac{\partial^2 L}{\partial \sigma_i^2 \partial \sigma_j^2} = \frac{1}{2} \text{ trace } (Z'_iPZ_jZ'_jPZ_i) - y'PZ_jZ'_jPZ_iZ'_iPy, \quad i,j = 0, 1 \ldots c \tag{27}$$

where $Z_0$ is defined as the unit matrix.

Expressions resulting from $i = 0$, $j = 0$ or both are also depending on the $W$-transforms only. For instance: $i = 0$ yields trace $(P)$ in (26), since from (8) $PV = (PVP)V = (PV)(PV)$, matrix $PV$ is idempotent and

$$\text{trace } (PV) = \text{rank } (PV) = \text{ rank } (P) = n - p, \text{ also}$$

$$\text{trace } (PV) = \sum_1^c \sigma_i^2 \text{ trace } (Z'_iPZ_i) + \sigma_0^2 \text{ trace } (P), \text{ hence}$$

$$\text{trace } (P) = \{n - p - \sum_1^c \sigma_i^2 \text{ trace } (Z'_iPZ_i)\}\sigma_0^{-2}. \tag{28}$$

Fisher's information matrix $-E[(\partial^2 L / \partial \sigma_i^2 \partial \sigma_j^2)]$ may be obtained from (27) and is given by the inverse of (22). Fisher's information matrix may be determined from the $W$-transforms $Z'_iPZ_j$.

When the REML estimates are positive they are a solution of the REML equations which are obtained by equating (26) to 0:

$$y'PZ_iZ'_iPy = \text{ trace } (Z'_iPZ_i), \quad i = 0, 1, \ldots c \tag{29}$$

The left-hand sides consist of quadratic forms depending on the unknown variance components. The right-hand sides are the corresponding expectations. It follows in particular that:

$$\hat{\sigma}_0^2 = (y - X\hat{\alpha})'\hat{H}^{-1}(y - X\hat{\alpha})/(n - p), \tag{30}$$

where $\hat{\alpha}$ is the estimator from (17).

When the model is formulated in terms of $\sigma_0^2$ and $\gamma_1 \ldots \gamma_c$, first and second order derivatives and Fisher's information matrix can also be obtained from the $W$-transforms $y'Py$, $y'PZ_i$, $Z'_iPZ_j$.

Finally, for later use, we will express the traces and sums of squares of observations in the first derivatives (26) and in Fisher's information matrix in terms of the solution and inverse of the coefficient matrix of the MMEs in (19). Elimination of $\alpha$ from (19) yields the following solution for the random effects:

$$\hat{b} = CZ'My,$$

where matrices $C$ and $M$ are defined in (7). The inverse of the coefficient matrix of the MMEs may be partitioned in correspondence with the fixed and random effects, matrix $C$ is the bottom right-hand part corresponding to the random effects. From (8) it may be shown that

$$\begin{aligned}
\text{trace}\,(Z'_iPZ_jZ'_jPZ_i) &= \lambda_i^2\lambda_j^2\sigma_0^{-4}\ \text{trace}\,(C_{ij}C_{ji}),\ i \neq j,\ i \neq 0,\ j \neq 0\\
\text{trace}\,(Z'_iPZ_iZ'_iPZ_i) &= \lambda_i^4\sigma_0^{-4}\ \text{trace}\,(C_{ii}^2) - 2\lambda_i^3\sigma_0^{-4}\ \text{trace}\,(C_{ii}) +\\
&\qquad q_i\lambda_i^2\sigma_0^{-4},\ i \neq 0\\
\text{trace}\,(Z'_iPZ_i) &= \lambda_i q_i\sigma_0^{-2} - \lambda_i^2\sigma_0^{-2}\ \text{trace}\,(C_{ii}),\ \ i \neq 0,
\end{aligned} \tag{31}$$

where $C = (C_{ij})$ is partitioned in correspondence with $b_1 \ldots b_c$. Furthermore

$$\begin{aligned}
y'PZ_iZ'_iPy &= \hat{b}'_i\hat{b}_i/\sigma_i^4,\ \ i = 1 \ldots c\\
y'Py &= (y'y - y'X\hat{\alpha} - y'Z\hat{b})/\sigma_0^2,
\end{aligned} \tag{32}$$

where $\hat{\alpha}, \hat{b}_1 \ldots \hat{b}_c$ are solutions of the MMEs (19).

## 6. Iterative procedures

### *6.1. Introduction*

Except for some particular models (Swallow and Monahan 1984 and Lee and Kapadia (1989) for the one-way random model and two-way mixed model with an equal number of observations for the levels of the random factor respectively) no closed expressions for REML estimates for an unbalanced layout are available. In this section some iterative procedures for finding the optimum of the REML likelihood (14) will be discussed. Emphasis will be on two methods: Fisher's method of scoring (section 6.2) and the EM-algorithm (section 6.3). Details of the actual calculations involved will be shown in section 7.

With the first and second order derivatives available from the $W$-transforms the field is wide open for any gradient method to find the optimum, see Harville (1977). A familiar, although not always reliable, method in statistics is Newton-Raphson. This method may be combined with (30) to reduce the dimension of the optimization problem (Corbeil and Searle, 1976a), resulting in a procedure zig-zagging between generalized least squares and Newton-Raphson (Jennrich and Sampson, 1976).

For models with $c = 1$ a one-dimensional search with respect to $\gamma_1 = \sigma_1^2/\sigma_0^2$ may be succesful, see Simianer (1988). For models with $c = 2$ in Smith and Graser (1986) a method is presented which combines a one dimensional search for the optimum of the likelihood with the EM-algorithm.

As in most non-linear optimization problems convergence to a global maximum is seldom guaranteed.

*6.2 Fisher scoring*

Suppose that the optimum of the REML likelihood corresponds to an inner point of the parameter space, i.e. the estimates are positive. Then the estimates will satisfy the REML equations (29). With (8) it follows that:

$$\text{trace } (Z'_iPZ_i) = \text{trace } (Z'_iPVPZ_i) = \sum_{j=0}^{c} \sigma_j^2 \text{ trace } (Z'_iPZ_jZ'_jPZ_i).$$

Hence, (29) may be written as:

$$[\text{trace } (Z'_iPZ_jZ'_jPZ_i)]\sigma^2 = (y'PZ_iZ'_iPy).$$

By evaluating the vector on the right-hand side and the matrix of traces on the left-hand side for the 'old' iterates and solving the set of linear equations for the 'new' iterates, an iterative procedure is obtained. In HARVILLE (1977) this method is referred to as Anderson's procedure.

From Fisher's information matrix (this is the inverse of (22)) and the gradient vector in (26), Anderson's procedure may be shown to be equivalent to Fisher's method of scoring. The same iteration process also results from iterating MINQUE and MIVQUE. Pros and cons of the method are:

pros:
- Generally reasonably fast (quadratic convergence),
- Fisher information readily available for inference.

cons:
- Iterates may be negative. During the iteration process they are usually replaced by small positive numbers, see for instance ROBINSON (1987a).
- The amount of calculation and storage required per iteration may be too large.

*6.3. EM-algorithm*

Write REML equations (29) as follows:

$$\frac{y'PZ_iZ'_iPy}{\text{trace } (Z'_iPZ_i)} = 1 \qquad i = 0, 1 \ldots c.$$

Multiplying both sides with $\sigma_i^2$, evaluating the left-hand side for the 'old' iterates and the right-hand side for the 'new' iterates, we end up with:

$$\sigma^2_{i[t+1]} = \left[\frac{y'PZ_iZ'_iPy}{\text{trace } (Z'_iPZ_i)}\right]_{[t]} \sigma^2_{i[t]}, \qquad i = 0, 1 \ldots c. \tag{33}$$

This may not look too impressive, but (33) is in fact a modified version of the EM-algorithm introduced in section 3.2. The procedure gains considerably in intuitive appeal when formulated in terms of the MMEs. The EM-algorithm as proposed by DEMPSTER et al. (1977; 1984) reads as follows:

$$\sigma^2_{i[t+1]} = [\hat{b}'_ib_i + \sigma_i^2\lambda_i \text{ trace } (C_{ii})]_{[t]}/q_i, \qquad i = 1 \ldots c \tag{34}$$

$$\sigma^2_{0[t+1]} = [\hat{e}'\hat{e} + \sigma^2_0(n - \sigma^2_0 \text{ trace } (P))]_{[t]}/n,$$

where the right-hand side is obtained under $\sigma^2 = \sigma^2_{[t]}$ and $\hat{e}$ is defined by (25). Combining 'old' and 'new' values for $\sigma^2_i$ on the right- and left-hand sides we obtain:

$$\sigma^2_{i[t+1]} = [\hat{b}'_i\hat{b}_i]_{[t]}/[q_i - \lambda_i \text{ trace } (C_{ii})]_{[t]}, \quad i = 1...c \tag{35}$$

$$\sigma^2_{0[t+1]} = [\hat{e}'\hat{e}]_{[t]}/[n - p - q + \sum_1^c \lambda_i \text{ trace } (C_{ii})]_{[t]},$$

using (28), and (31) for trace $(P)$. Expressions in (33) and (35) may be shown to be equivalent with the help of (31) and (32). The algorithm (34) is referred to by HARVILLE (1977) as Henderson's procedure. HENDERSON (1986a,b,c) derived (34) from MIVQUE quadratics.

The expression for $\sigma^2_0$ in (35) may be found in MEYER (1987). HARVILLE (1977) gives a different expression:

$$\sigma^2_{0[t+1]} = y'M[y - Z\hat{b}]_{[t]}/(n - p) = [y'\hat{e}]_{[t]}/(n - p). \tag{36}$$

At convergence the difference between $\sigma^2_{o[t+1]}$ from (35) and (36) vanishes to zero. A numerically attractive expression for $\sigma^2_{0[t+1]}$ follows from:

$$\hat{e}'\hat{e} = y'\hat{e} - \hat{b}'D^{-1}\hat{b} = y'y - y'X\hat{\alpha} - y'Z\hat{b} - \hat{b}'D^{-1}\hat{b}. \tag{37}$$

Pros and cons of the EM-algorithm are:

pros:
- The computational burden and amount of storage required per iteration may be considerably less than for Fisher scoring. Fisher scoring, formulated in terms of the MMEs, additionally to trace $(C_{ii})$ also needs traces of the off-diagonal parts of $C$: trace $(C_{ij})$, $i \neq j$.
- Shares some good properties with all EM-algorithms, for instance the likelihoods corresponding to the successive iterates will not decrease, see DEMPSTER et al. (1977).
- From the formulae in section 3.2 it easily follows that, starting from positive values, negative iterates will never be encountered. The same holds for (35) (HARVILLE, 1977).
- Considerable intuitive appeal.

cons:
- Slow, sometimes very slow, especially when the optimum is near the boundary of the parameter space, see LAIRD and WARE (1982) and DEMPSTER et al. (1977) (R. Thompson in the discussion and the reply by the authors). The algorithm may be speeded up, see THOMPSON and MEYER (1986).

## 7. How to perform the calculations

### *7.1. Introduction*

Broadly speaking there are two sources of literature on the numerical side of parameter estimation in a mixed model: papers of a general statistical nature and papers directed at animal breeding research.

In the statistically orientated papers emphasis is on the $W$-transforms for use in a gradient method to obtain ML or REML estimates or to solve the MINQUE or MIVQUE equations, see Hemmerle and Hartley (1973), Thompson (1975), Jennrich and Sampson (1976), Corbeil and Searle (1976a), Hemmerle and Lorens (1976), Liu and Senturia (1977), Goodnight and Hemmerle (1979), Giesbrecht (1983) and Giesbrecht (1986). In Goodnight and Hemmerle (1979) and Giesbrecht (1983) similar algorithms using sweep-operations are described. The use of sweep-operations will be discussed in section 7.2.

In animal breeding emphasis is on the mixed model equations. Popular methods are Fisher scoring and the EM-algorithm. Numerical reductions are obtained by elimination of sets of effects from the MMEs. This process is referred to as absorption. Because of the large size of datasets in animal breeding, the need for reduction of the size of matrices to be stored and/or inverted is particularly pressing, see Meyer and Burnside (1987), Meyer (1986a,b, 1987), Smith and Graser (1986). The use of absorption will be discussed in section 7.3.

To what extent numerical reduction is possible depends on the structure of the data: nesting is usually a favourable type of structure. In completely nested designs only diagonal matrices have to be inverted, see Giesbrecht (1978), Longford (1980, 1986, 1987), Kleffe and Seifert (1984) and Rao and Kleffe (1988).

### *7.2. Sweeping a working matrix*

The following working matrix is introduced:

$$\Omega = \begin{bmatrix} Z'Z+D^{-1} & Z'Z & Z'X & Z'y \\ Z'Z & Z'Z & Z'X & Z'y \\ X'Z & & X'X & X'y \\ y'Z & \text{symm.} & & y'y \end{bmatrix} \sigma_0^{-2}. \tag{38}$$

Partial Gaussian Elimination on the upper left-hand part yields for the lower right-hand part:

$$\left[ \begin{bmatrix} Z'Z & Z'X & Z'y \\ & X'X & X'y \\ \text{symm.} & & y'y \end{bmatrix} - \begin{bmatrix} Z'Z \\ X'Z \\ y'Z \end{bmatrix} (Z'Z+D^{-1})(Z'Z,\ Z'X,\ Z'y) \right] \sigma_0^{-2},$$

which, from (6) and (8), is equal to:

$$\begin{bmatrix} Z'V^{-1}Z & Z'V^{-1}X & Z'V^{-1}y \\ & X'V^{-1}X & X'V^{-1}y \\ \text{symm.} & & y'V^{-1}y \end{bmatrix}.$$

Application of a sweep operator, see for instance EFROYMSON (1960), pivoting on the elements of $X'V^{-1}X$, using (7), yields:

$$\begin{bmatrix} Z'PZ & -Z'V^{-1}X(X'V^{-1}X)^{-1} & Z'Py \\ & (X'V^{-1}X)^{-1} & (X'V^{-1}X)^{-1}X'V^{-1}y \\ \text{symm.} & & y'Py \end{bmatrix}.$$

All elements of this matrix are of interest: the $W$-transforms $Z'PZ=(Z'_iPZ_j)$, $Z'Py=(Z'_iPy)$ and $y'Py$, the generalized least squares estimator $(X'V^{-1}X)^{-1}X'V^{-1}y$, the corresponding variance-covariance matrix $(X'V^{-1}X)^{-1}$ and finally $Z'V^{-1}X(X'V^{-1}X)^{-1}$, which is used for the calculation of the approximate number of degrees of freedom in the $t$-test of GIESBRECHT and BURNS (1985) presented in section 4.1. For an introduction to Gaussian Elimination and sweeping see GOODNIGHT (1979).

As a by-product, from the products of the pivot elements, we have the determinants $|Z'Z+D^{-1}|$ and $|X'V^{-1}X|$. Since

$$|X'X||Z'MZ+D^{-1}|=|Z'Z+D^{-1}||X'V^{-1}X|\,\sigma_0^{2p},$$

we are also able to evaluate the log likelihood (15) up to an (unimportant) constant.

Following GOODNIGHT and HEMMERLE (1979) the operations may be performed efficiently with minimum storage with respect to the working matrix $\Omega$ in (38). Small values of variance components may give rise to numerically dangerously high pivot elements. In the approach followed by GOODNIGHT and HEMMERLE (1979) these pivots are recognisable throughout the Gaussian Elimination proces. Appropriate action, originally suggested by a referee of HEMMERLE and HARTLEY (1973), may be taken. Small pivot elements are numerically unacceptable as well and a pivot strategy, see DAHLQUIST and BJÖRCK (1974), restricted to the diagonal elements, may be followed. We will return to sweeping procedures in section 7.4.

### *7.3 Absorption*

#### *7.3.1 Definition and properties.*

For the set of equations

$$\begin{bmatrix} A_{11} & A_{12} \\ A_{21} & A_{22} \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} y_1 \\ y_2 \end{bmatrix}$$

elimination of vector $x_1$ from the upper part of the set yields:

$$x_1 = A_{11}^{-1}(y_1 - A_{12}x_2).$$

Substitution in the lower part of the set yields a set of equations in $x_2$:

$$(A_{22} - A_{21}A_{11}^{-1}A_{12})x_2 = y_2 - A_{21}A_{11}^{-1}y_1. \tag{39}$$

The equations for $x_1$ are now absorbed into the equations for $x_2$.

Some properties:

(i) Let $A=(A_{ij})$ and $B=(B_{ij})=A^{-1}$. The coefficient matrix of $x_2$ after absorption of $x_1$ is $B_{22}^{-1}$, i.e. $B_{22}=(A_{22}-A_{21}A_{11}^{-1}A_{12})^{-1}=A_{22}^{-1}+A_{22}^{-1}A_{21}[A_{11}-A_{12}A_{22}^{-1}A_{21}]^{-1}A_{12}A_{22}^{-1}$. The expression on the right-hand side between square brackets is the coefficient matrix of $x_1$ after absorption of $x_2$.

(ii) For $k$ sets of equations $Ax=y$, $A=(A_{ij})$, $x=(x_i)$, $y=(y_i)$, absorb vectors $x_1 \ldots x_m$, $m<k$. Let the resulting set of equations in $x^*=(x'_{m+1} \ldots x'_k)'$ be $A^*x^*=y^*$. Let $B=(B_{ij})=A^{-1}$ and $B^*=(B_{ij}{}^*)=A^{*-1}$, then $B_{ii}=B_{ii}{}^*$, $i=m+1 \ldots k$.

Typically the set of equations will be the mixed model equations (19), vectors $x_1, x_2 \ldots$ will correspond to sets of fixed effects and random effects. Basically sweeping and absorption are equivalent, sweeping on the diagonal elements of $A_{11}$ yields for the lower right-handside of $A$ the coefficient matrix of (39), see MOHAMMAD et al. (1985).

### *7.3.2. Reducing the size of matrices to be stored and inverted.*

Let $F$ be a factor with a very large number of levels. Let $G$ be the collection of all parameters in the model corresponding with $F$ and interactions with $F$. Suppose that the number of elements in $G$ prohibits storage of the mixed model equations and inversion of the coefficient matrix. It will be shown that the set of equations after absorption of the elements of $G$ may be constructed in one pass through the data, reading the data one level of $F$ at a time. In a second pass through the data the complete solution of the MMEs is obtained by back substitution. Quadratic forms in the observations and traces of matrices for the iteration proces may be obtained without any need for storage and inversion of large matrices. When the reduced set of equations is still too large further reduction may be possible. This will be discussed briefly in section 7.3.3.

Let $F$ correspond to a random effect. For a fixed effect a similar approach may be followed. In the latter case $G$ should correspond to nuisance parameters since variances and covariances involving estimators of parameters in $G$ are lost, see ROBINSON (1987a).

Let $Z=(Z_1,Z_2)$, $D=\text{diag}(D_1,D_2)$, $b=(b'_1,b'_2)'$, where $Z_1, D_1$ and $b_1$ correspond to $G$. Absorption of $b_1$ from the MMEs yields

$$\begin{bmatrix} X'KX & X'KZ_2 \\ Z'_2KX & Z'_2KZ_2+D_2^{-1} \end{bmatrix} \begin{bmatrix} \alpha \\ b_2 \end{bmatrix} = \begin{bmatrix} X'Ky \\ Z'_2Ky \end{bmatrix}, \tag{40}$$

where $K=I-Z_1(Z'_1Z_1+D_1^{-1})^{-1}Z'_1$. Matrices $Z_1$ and $D_1$ are block diagonal, blocks corresponding to levels of $F$. Matrix $K$ will be block diagonal as well:

$$Z_1=\text{diag}(Z_{1i}),\ D_1=\text{diag}\,(D_{1i}),\ K=\text{diag}\,(K_i),$$

where $K_i=I_{m_i}-Z_{1i}(Z'_{1i}Z_{1i}+D_{1i}^{-1})^{-1}Z'_{1i}$ is an $m_i\times m_i$ matrix, with $m_i$ the number of observations associated with the $i$-th level of $F$. Let the total number of levels of $F$ be $m$ and partition $X$, $Z_2$ and $y$ correspondingly:

$$X=(X'_1\ldots X'_m)',\ Z_2=(Z'_{21}\ldots Z'_{2m})',\ y=(y'_1\ldots y'_m)'$$

Then

$$X'KX=\sum_i X'_iK_iX_i,\quad X'KZ_2=\sum_i X'_iK_iZ_{2i},\quad Z'_2KZ_2=\sum_i Z'_{2i}K_iZ_{2i},$$

$$X'Ky=\sum_i X'_iK_iy_i,\quad Z'_2Ky=\sum_i Z'_{2i}K_iy_i.$$

Hence, (40) may be constructed by reading the data one level of $F$ at a time, cumulating the results. Let $N=(N_{ij})$ be the symmetric inverse of the coefficient matrix of (40), i.e.:

$$\begin{bmatrix} \hat{a} \\ \hat{b}_2 \end{bmatrix} = \begin{bmatrix} N_{11} & N_{12} \\ N_{21} & N_{22} \end{bmatrix} \begin{bmatrix} X'Ky \\ Z'_2Ky \end{bmatrix}. \tag{41}$$

Partitioning $b_1$ in correspondence with the levels of $F$, $b_1=(b'_{11}\ldots b'_{1m})'$ follows in a second pass through the data from:

$$\hat{b}_{1i}=(Z'_{1i}Z_{1i}+D_{1i}^{-1})^{-1}\ Z'_{1i}(y_i-X_i\hat{\alpha}-Z_{2i}\hat{b}_2).$$

Quadratic forms follow from (32). From (31), for Fisher scoring or the EM-algorithm, we need traces of parts of matrix $C$, the inverse of the coefficient matrix of the MMEs after absorption of the fixed effects. For notational convenience let $b_2$ correspond to a single additional random factor, i.e. $c=2$. Partitioning $C=(C_{ij})$ in correspondence with $b_1$ and $b_2$, matrix $C_{22}$ is equal to $N_{22}$ in (41). We still have to determine traces involving $C_{11}$, $C_{11}^2$ and $C_{12}C_{21}$. As an illustration trace $(C_{11})$ will be determined, for the other traces a similar approach may be followed. From properties (i) and (ii) in section 7.3.1:

$$C_{11}=B^{-1}+B^{-1}(Z'_1X,Z'_1Z_2)\left[\begin{bmatrix} X'X & X'Z_2 \\ Z'_2X & Z'_2Z_2+\lambda_2I \end{bmatrix}-\begin{bmatrix} X'Z_1 \\ Z'_2Z_1 \end{bmatrix}B^{-1}(Z'_1X,Z'_1Z_2)\right]^{-1}\begin{bmatrix} X'Z_1 \\ Z'_2Z_1 \end{bmatrix}B^{-1}$$

where $B=Z'_1Z_1+\lambda_1I$. $B$ is a diagonal matrix and easy to invert. The matrix

between square brackets is, according to property (i), the coefficient matrix after absorption of $b_1$. This is the coefficient matrix of (40) and the inverse is matrix $N$ from (41). hence:

$$C_{11} = B^{-1} + B^{-1}[Z'_1 X N_{11} X' Z_1 + Z'_1 X N_{12} Z'_2 Z_1 + Z'_1 Z_2 N_{21} X' Z_1 + Z'_1 Z_2 N_{22} Z'_2 Z_1] B^{-1}.$$

Multiplying each of the terms between square brackets from both sides with $B^{-1}$, the trace of $C_{11}$ will be a sum of five traces. One of these traces is:

$$\text{trace}\,(B^{-1} Z'_1 X N_{11} X' Z_1 B^{-1}) = \text{trace}\,(N_{11} X' Z_1 B^{-2} Z'_1 X).$$

Since

$$X' Z_1 B^{-2} Z'_1 X = \sum_i X'_i Z_{1i} (Z'_{1i} Z_{1i} + \lambda_1 I_{m_i})^{-2} Z'_{1i} X_i,$$

the trace may be determined in the second pass through the data.

*7.3.3. Further reductions.*

In animal breeding datasets may be very large: in MEYER and BURNSIDE (1987) for instance, a data set is reported consisting of observations on 131890 cows from 599 sires (a random factor in the model) on 3924 farms (traditionally a fixed factor in the model).

We will have a brief look at an example from MEYER (1987). Offspring is observed ($y$) from sires ($b_1$) and dams ($b_2$). Animals are housed at different farms ($\alpha_1$) and observations are collected in different seasons and years ($\alpha_2$). Suppose that the number of farms and dams is very large. Sires may be related and dams may be related, i.e. matrices $A_i$ from (2) are not equal to the identity matrix. Suppose that dams are nested within farms and farms may be divided into $m$ distinct groups such that animals from different groups are unrelated. In one pass through the data, reading the observations one dam within a group of farms at a time, the reduced set of MMEs after absorption of dams and farms may be constructed and solved. The full solution follows from back substitution in a second pass through the data. For the EM-algorithm sums of squares such as $\hat{b}'_i A_i^{-1} b_i$ and traces of matrices $A_i^{-1} C_{ii}$ are needed. Matrices $A_i$ are block diagonal and inverses $A_i^{-1}$ follow from HENDERSON (1976) and QUAAS (1976). $\hat{b}'_1 A_1^{-1} \hat{b}_1$ follows from direct calculation and $\hat{b}'_2 A_2^{-1} \hat{b}_2$ from the second pass through the data:

$$\hat{b}'_2 A_2^{-1} \hat{b}_2 = \sum_j \hat{b}_{2j} A_{2j}^{-1} \hat{b}_{2j}, \text{ index } j \text{ corresponding to groups of farms.}$$

Similarly

$$\hat{e}'\hat{e} = \sum_j \hat{e}'_j \hat{e}_j, \text{ where } \hat{e}_j = y_j - X_{1j}\hat{\alpha}_{1j} - X_{2j}\hat{\alpha}_2 - Z_{1j}\hat{b}_1 - Z_{2j}\hat{b}_{2j},$$

with $X_1 = \text{diag}\,(X_{1j})$ and $X_2 = (X'_{21} \ldots X'_{2m})'$ corresponding to $\alpha_1$ and $\alpha_2$

respectively, $Z_1=(Z'_{11}...Z'_{1m})'$ and $Z_2=\text{diag}(Z_{2j})$. The trace of $A_1^{-1}C_{11}$ follows from direct calculation. The calculation of trace $(A_2^{-1}C_{22})$ is very cumbersome indeed, taking several pages of algebra. For a detailed account see ENGEL (1989).

*7.4. Where sweeping and absorption meet*

In SMITH and GRASER (1986) for models with $c=2$ and under restriction (9) REML estimates are obtained by a combination of sweeping and absorption. The model is re-formulated as:

$$y=X\alpha+Z_1b_1+e^*, \text{ where } e^*=Z_2b_2+e \text{ and} \qquad (42)$$
$$\text{Var}(e^*)=R\sigma_0^2 \text{ with } R=\gamma_2Z_2Z'_2+I_n.$$

The estimation procedure consists of two steps. In the 'interior-step' $\gamma_2$ is kept fixed and $\sigma_0^2$, $\sigma_1^2$ are estimated by the EM-algorithm applied to (42). In the 'exterior-step' the optimum of the likelihood corresponding to $\gamma_2$, say $l(\gamma_2)$, is determined and $l(\gamma_2)$ is optimised with a grid-search or other one-dimensional search routine, see SIMIANER (1988). Expressions for the log likelihood and the EM-algorithm may be obtained from (15) and (35) respectively with the help of transformation (10). The interior step involves a large number of iteration steps for the EM-algorithm. In this step partial Gaussian Elimination on a working-array is used. A factor with a large number of levels may be absorbed. The computational burden is considerably reduced by the use of tri-diagonalisation (see STOER and BULIRSCH (1973) or PRESS et al. (1986)).

## 8. THINGS STILL TO BE DONE

For inference on components of variance (section 4.2), except for some particular models, little progress has been made. Little is known about the small sample behaviour of the normal approximation. In fact there does not seem to be any paper dealing with the asymptotics of REML-estimators directly.

For sets of fixed effects, tests and confidence regions may be derived from a chi-square approximation of (Wald-test): $(\hat{\alpha}_0-\alpha_0)'\widehat{\text{Var}}(\hat{\alpha}_0)^{-1}(\hat{\alpha}_0-\alpha_0)$, where $\alpha_0$ is a sub-vector of $\alpha$. In this procedure estimation of $\text{var}(\hat{\alpha}_0)$ by $\text{Var}(\hat{\alpha}_0)$, by substitution of the REML estimates, is not taken into account. For a single contrast an $F$-distribution may be used (the square of the approximate $t$-distribution in section 4.1). For multiple contrasts no similar approach is available yet.

The relationship between iterated MINQUE and REML makes it plausible that REML may be robust against departures from Normality. At present only limited simulation results from LIN and MCALLISTER (1984) seem to be available.

Little is known about sensitivity of REML to outliers. For a robust approach in this respect see FELLNER (1986).

There are computer routines available for REML in some of the larger

statistical packages such as SAS and BMDP. Probably the most useful general purpose program at present is the REML program from the Scottish Agricultural Statistics Service in Edinburgh (ROBINSON, 1987a). At present facilities for testing in this program are limited to a normal approximation for single contrasts. There are no facilities within the program for data-handling such as for instance the use of a log transformation. For models relevant to animal breeding, programs from *K.* Meyer and from L.R. Schaeffer are circulating. These specialised programs are able to handle very large data sets.

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# Chapter 3

## Analysis of embryonic development with a model for under- or overdispersion relative to binomial variation

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A discussion of quasi-likelihood estimation and under- and over-dispersion in the context of a practical example. Estimation with IRREML for non-normal data shares properties with maximum quasi-likelihood estimation. Moreover, some over-dispersion models, e.g. Williams' model III, are special cases of GLMMS, where residual errors on the link scale are integrated out.

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# Analysis of Embryonic Development with a Model for Under- or Overdispersion Relative to Binomial Variation

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SUMMARY

Observations from a study of the development of ovulations into embryos for Texel sheep are analysed with a model for count data that are under- or overdispersed relative to binomial variation. The analysis is based on maximum quasi-likelihood (McCullagh and Nelder, 1989, *Generalized Linear Models*, 2nd edition, London: Chapman and Hall), following an approach suggested by Williams (1982, *Applied Statistics* **31**, 144–148). The dispersion parameter is developed as a combination of a variance component representing shared maternal effects and a correlation, typically negative, between ovulations within ewes. The number of ovulations (the binomial denominator) is included as an explanatory variable.

## 1. Introduction

In an experiment conducted at the Research Institute for Animal Production "Schoonoord" in The Netherlands, the effects of active immunisation against androstenedione on the fertility of Texel ewes are studied. The number of fetuses per ewe can be considered as the net result of a process determining the number of ovulations and a probability process for these ovulations to yield fetuses. In this paper the second process will be modelled and the number of fetuses will be analysed in relation to treatment with Fecundin (androstenedione-7$\alpha$-carboxyethylthioether:HSA), age of the animal, mating period, and number of ovulations observed.

An outline of the experiment and a summary of the data are given in the next section. The full data set is presented in Appendix A.1. The model, introduced in Section 3, accounts for random variation in embryonic development rate between ewes and correlation (typically negative for this problem) between ovulations within ewes. No full distributional assumptions are made; only the first two moments will be specified. In Section 4 estimation and testing of parameters will be discussed. Parameters will be estimated by a combination of maximum quasi-likelihood for location on the logit scale (§4.1) and a method of moments for dispersion (§4.2), utilizing the relationship between expectations and variances. Details of the iterative procedure are provided in Appendices A.2 and A.3. Results of the analysis are presented in Section 5, where an attempt is made to substantiate the supposition that the data are underdispersed relative to binomial variation. Finally, in Section 6, some alternative approaches are discussed.

Perhaps because of the opposing effects of overdispersion from shared maternal effects and underdispersion from negative correlation between ovulations within ewes, qualitative results were rather similar to those obtained from an ordinary logit analysis for independent binomial data. However, the more involved analysis, motivated by the biological background of the model, had to be undertaken to find out. Furthermore, the approach is not so difficult that it should not be used fairly routinely when a binomial distribution is in doubt.

*Key words:* Beta–binomial distribution; Beta–correlated-binomial distribution; Correlated binomial logistic model; Embryonic development rate; Extra-binomial variation; Maximum quasi-likelihood; Overdispersion; Ovulations; Underdispersion; Williams Model II.

## 2. The Experiment

From 125 Texel ewes, 63 ewes are treated with Fecundin (kindly donated by Coopers Agrovet B.V. Haarlem, The Netherlands). The remaining 62 serve as a control group. The ewes are classified into four age classes (≤.5, .5–1.5, 1.5–2.5, >2.5 years) and there are two mating periods (starting on October 1 and October 22, 1986, respectively). Interactions with age are of interest and since a factor is easier to handle in this respect than a covariable, age was introduced as a factor. Moreover, it is difficult to decide on a proper curve representing age effects, when age is introduced as a covariable. The numbers of animals in the four age classes are 25, 44, 24, and 32, respectively. The ewes per age class are about evenly spread over the combinations of mating periods and treatment groups.

The ewes are slaughtered 75–80 days after last mating and the number of ovulations and the number of fetuses are determined. Ovulation numbers range from 1 to 5. For six animals the number of ovulations is not known. These ewes are excluded from the analysis. The raw means and standard deviations of the percentages of ovulations yielding fetuses—i.e., averages of ratios of number of fetuses and ovulations per ewe multiplied by 100%—are shown in Table 1.

In a separate analysis, not to be discussed in this paper, it was shown that the number of ovulations (and fetuses) is increasing with age and treatment with Fecundin (Te Brake and Oosterom, unpublished manuscript). This will be useful later when the results of the analysis are to be interpreted.

**Table 1**
*Means and standard deviations (in parentheses) of the percentage of ovulations yielding a fetus and estimated means and standard errors (in parentheses) from the analysis*

| Mating period | Treatment | Age class (years) | Raw mean % | Number of animals | Estimated mean % |
|---|---|---|---|---|---|
| Oct. 1 | Fecundin | ≤.5 | 83 (26) | 6 | 82 (11) |
| | | .5–1.5 | 75 (28) | 10 | 72 (8) |
| | | 1.5–2.5 | 78 (25) | 6 | 81 (9) |
| | | >2.5 | 81 (22) | 6 | 82 (9) |
| | Control | ≤.5 | 80 (27) | 5 | 70 (17) |
| | | .5–1.5 | 80 (23) | 11 | 78 (8) |
| | | 1.5–2.5 | 86 (22) | 6 | 86 (8) |
| | | >2.5 | 94 (18) | 8 | 94 (5) |
| Oct. 22 | Fecundin | ≤.5 | 64 (24) | 7 | 58 (14) |
| | | .5–1.5 | 71 (25) | 11 | 72 (8) |
| | | 1.5–2.5 | 78 (30) | 6 | 75 (8) |
| | | >2.5 | 88 (23) | 7 | 81 (7) |
| | Control | ≤.5 | 100 (0) | 6 | 100 (1) |
| | | .5–1.5 | 95 (15) | 11 | 95 (5) |
| | | 1.5–2.5 | 83 (6) | 6 | 83 (10) |
| | | >2.5 | 93 (7) | 7 | 94 (5) |

## 3. The Model

For each ewe let $n$ = the number of ovulations, $x$ = the number of fetuses, and $p$ = the probability of an ovulation yielding a fetus. Inference about the number of fetuses $x$ will be conditional upon the values observed for the number of ovulations $n$. The probability $p$ will be the quantity of interest in the analysis. For each of the ovulations within a ewe an indicator variable is defined:

$$a_k = \begin{cases} 1, & \text{when the } k\text{th ovulation yields a fetus,} \\ 0 & \text{otherwise, } k = 1, 2, \ldots, n. \end{cases}$$

Hence, $x = a_1 + \cdots + a_n$, the number of ovulations yielding fetuses. The probability $p$ will depend on treatment ($T$), age class ($A$), mating period ($M$), and on the particular ewe:

$$p = p_0 + \epsilon.$$

The fixed part $p_0$ is determined by the factors $T$, $A$, and $M$, and the random part $\epsilon$ represents the contribution of the ewe. It is assumed that $\epsilon$ has expectation 0 and small variance when $p_0$ is close to 0 or 1 and larger variance when $p_0$ is close to .5. A simple variance function meeting these requirements is

$$\text{var}(\epsilon) = \sigma^2 p_0(1 - p_0). \tag{1}$$

Of course there are many other possibilities, e.g., when the ewe effect is introduced with constant variance $\sigma^2$ on the logit scale, such as in Williams Model III (Williams, 1982), $\text{var}(\varepsilon) = \sigma^2(p_0(1 - p_0))^2$ approximately. Since it is hard to choose between these variance functions, neither from the physical background of the problem, nor from plots of residuals, we will adopt the simple variance function (1). The scale parameter $\sigma^2$ is assumed to be relatively small. No detailed assumptions about the distribution of $p$ are made. The beta distribution (Johnson and Kotz, 1970, Chap. 24) would be a candidate. In that case for a (skewed) bell-shaped distribution $\sigma^2$ will have to satisfy $\sigma^2 < \frac{1}{3}$.

We will allow for some "competition" between the ovulations. Suppose that conditional on $\varepsilon$ (i.e., given the value of the ewe effect), $\rho$ is the correlation between $a_k$ and $a_{k'}$:

$$\text{cov}(a_k; a_{k'}|\varepsilon) = \rho p(1 - p), \quad k, k' = 1, 2, \ldots, n; \quad k \neq k'.$$

Typically $\rho$ will be negative. It is assumed that $\rho$ is constant, i.e., independent of $n$ and $p$, and not too far from 0. A proper variance–covariance structure for the indicator variables $a_1, \ldots, a_n$ implies at least that $\rho$ must satisfy $\rho > -1/(n_{\max} - 1)$, where $n_{\max}$ is the largest number of ovulations in the data set. Clearly, for a wide range of values for $n$, the assumption of constant $\rho$ would not have been tenable. For the limited numbers of ovulations in the present problem it does not seem to be an unreasonable assumption.

The fixed part $p_0$ of $p$ may also depend on the number of ovulations $n$. Since the data set does not allow for a very complicated model, the following simplification will be made. Additional to factors $T$, $A$, and $M$, a factor $N$ (short for "number") is introduced with two levels corresponding to $n \leqslant 2$ and $n \geqslant 3$, respectively. The fixed part $p_0$ may thus depend on factors $T$, $A$, $M$, and $N$.

For modelling $p_0$ we will use the logit function, which conveniently stretches the interval (0, 1) to the whole real line $(-\infty, +\infty)$:

$$\begin{aligned} \text{logit}(p_0) &= \log(p_0/(1 - p_0)) \\ &= \text{Grand mean} + \text{Main effects} + \text{Interactions of } T, A, M, \text{ and } N. \end{aligned} \tag{2}$$

Since we cannot afford a large number of parameters, no interactions with the factor $N$ will be considered. Grand mean, main effects, and interactions are similar to analysis of variance, except that they are introduced on a logit scale.

For the expectation and variance of the number of fetuses $x$ we have

$$\text{E}(x) = np_0, \quad \text{var}(x) = np_0(1 - p_0)(1 + (n - 1)\phi), \tag{3}$$

where $\phi = \rho + (1 - \rho)\sigma^2$ is the unconditional (with respect to $\varepsilon$, the contribution of the ewe) correlation between any two indicator variables $a_k$ and $a_{k'}$, $k \neq k'$, within the same ewe. Observe that the variance under the binomial distribution corresponds to $\phi = 0$. The "overall" correlation $\phi$ may be either positive (overdispersion relative to binomial variation) or negative (underdispersion). This will depend on the relative sizes of the overdispersion introduced by the ewe effect $\varepsilon$ (between-ewe variation), represented by $\sigma^2$, and the underdispersion introduced by the (conditional) correlation $\rho$ (within-ewe "competition").

## 4. The Analysis

### 4.1 *Known Dispersion Parameter* $\phi$

For the moment we will make the unrealistic assumption that the correlation $\phi$ is known. We will drop this assumption later. The relationship between the expectation and the variance of the number of fetuses $x$ in (3) is now completely known. This is all that is needed for estimation of the grand mean, main effects, and interactions in $\text{logit}(p_0)$ in (2) by the method of maximum quasi-likelihood (MQL). MQL is discussed extensively in McCullagh and Nelder (1989, Chap. 9), and will be discussed briefly below.

A simple derivation of the algorithm for quasi-likelihood estimation is as follows. Let $p_*$ be an a priori value (a guess) for $p_0$. Then

$$\text{E}(x) = np_0 \approx np_* + n\left(\frac{\partial p}{\partial \boldsymbol{\beta}}\right)_{\boldsymbol{\beta}_*}' (\boldsymbol{\beta}_0 - \boldsymbol{\beta}_*) = np_* + np_*(1 - p_*)\mathbf{b}'(\boldsymbol{\beta}_0 - \boldsymbol{\beta}_*),$$

where vector $\boldsymbol{\beta}_0$ denotes the true values for the grand mean, main effects, and interactions corresponding to $p_0$ and likewise $\boldsymbol{\beta}_*$ corresponds to $p_*$, i.e., $\text{logit}(p_0) = \mathbf{b}'\boldsymbol{\beta}_0$, where the known vector $\mathbf{b}$ follows from the design of the experiment and corresponds to the ewe concerned. A new (artificial) dependent variable $y$ is defined:

$$y = ((x - np_*)/v_*) + \mathbf{b}'\boldsymbol{\beta}_* \quad \text{with } v_* = np_*(1 - p_*).$$

Now $E(y) \approx \mathbf{b}'\boldsymbol{\beta}_0$ and $\text{var}(y) \approx 1/(wv_*)$, where $w = 1/(1 + \phi(n - 1))$. With weighted linear regression for $y$ an improved estimator for $\boldsymbol{\beta}_0$ may be derived. The improved estimator becomes the new $\boldsymbol{\beta}_*$ and the calculations are repeated until subsequent values are alike.

In each step of the algorithm the following set of normal equations is solved, introducing indices $i = 1, \ldots, m$ for the units and $j = 1, \ldots, q$ for the location parameters in $\boldsymbol{\beta}$:

$$\sum_{i=1}^{m} (y_i - \mathbf{b}_i'\boldsymbol{\beta})w_i v_{*i} b_{ij} = 0, \quad j = 1, \ldots, q,$$

where $b_{ij}$ is the $j$th element of vector $\mathbf{b}_i$ and the $(i, j)$th element of the design matrix. It is not hard to see from the definition of $y$ that the algorithm is actually solving

$$\sum_{i=1}^{m} (x_i - n_i p_{0i})/(1 + \phi(n_i - 1))b_{ij} = 0, \quad j = 1, \ldots, q. \tag{4}$$

This is a particular instance of the more general set of quasi-likelihood equations:

$$\sum_{i=1}^{m} \frac{x_i - \mu_i}{\sigma_i^2}\left(\frac{\partial \mu_i}{\partial \eta_i}\right) b_{ij} = 0, \quad j = 1, \ldots, q,$$

where $\mu_i = E(x_i)$, $\eta_i = g(\mu_i) = \mathbf{b}_i'\boldsymbol{\beta}$, with $g$ the link function and $\eta_i$ the linear predictor, $\sigma_i^2 = \text{var}(x_i)$; $\sigma_i^2$ may depend on $\mu_i$, i.e., $\sigma_i^2 = \sigma_i^2(\mu_i)$. For the present model: $\mu = np_0$, $\eta = \text{logit}(\mu/n) = \log(\mu/(n - \mu))$, $\partial\mu/\partial\eta = \mu(n - \mu)/n$.

The final estimates correspond to a stationary point, hopefully the maximum, of Wedderburn's (1974) quasi-likelihood function. The left-hand sides of expression (4) correspond to the partial derivatives of the quasi-likelihood with respect to the elements of $\boldsymbol{\beta}$. Formally the quasi-likelihood $Q$ can be defined as

$$Q = \sum_{i=1}^{m} \int_{x_i}^{n_i} (x_i - t)/\sigma_i^2(t)\, dt,$$

and for the model discussed in this paper:

$$\begin{aligned} Q &= \sum_i n_i/(1 + \phi(n_i - 1)) \int_{x_i}^{n_i p_{0i}} (x_i - t)/(t(n_i - t))\, dt \\ &= \sum_i (1 + \phi(n_i - 1))^{-1}(L(n_i p_{0i}; x_i, n_i) - L(x_i; x_i, n_i)), \end{aligned} \tag{5}$$

where $L(t; x, n) = x \log(t/n) + (n - x)\log((n - t)/n)$.

The algorithm used is the same as for generalized linear models (GLM) (Nelder and Wedderburn, 1972) for maximum likelihood estimation and a generalisation of an algorithm described in Finney (1947, Appendix II) for biological assay. Therefore in a GLM, with a probability distribution from the exponential family—e.g., normal, binomial, or Poisson—quasi-likelihood and maximum likelihood estimators are the same. For $\phi = 0$ for the present model, quasi-likelihood is equivalent to an ordinary logit analysis (Cox, 1970, §2.3).

The calculations are easily performed with the algorithm for GLM models in GENSTAT 5 (GENSTAT 5 Committee, 1987, 1990), when the error distribution is specified as binomial with a logit link function and prior weights $(1 + \phi(n - 1))^{-1}$. The GENSTAT code is given in Appendix A.3. A similar code in GLIM is given by Williams (1982).

Maximum quasi-likelihood estimators share many of the (asymptotic) properties of maximum likelihood estimators, as shown in McCullagh (1983). In the same paper the quasi-likelihood ratio (QLR) test is discussed. The QLR statistic may be used to see whether various subsets of the parameters, e.g., the parameters for the interaction $T.A$ between factors $T$ and $A$, contribute significantly to the model. Under the null hypothesis $H_0$: $T.A = 0$, the QLR statistic may be compared with a chi-square distribution with degrees of freedom equal to the reduction of free parameters: $(2 - 1)(4 - 1) = 3$.

With GENSTAT, the QLR statistic is easily derived from the difference between the deviance under the restricted model ($T.A = 0$) and the model under investigation (including $T.A$); see Appendix A.3. For a GLM the deviance $D$ is defined as minus twice the difference between the log-likelihood of the model under investigation and the maximum achievable value for the log-likelihood obtained by replacing the expectation $\mu$ of each observation $x$ by the observation itself:

$$D = -2(L(\mu; x) - L(x; x)),$$

where $L$ denotes the log-likelihood. Replacing $\mu$ by its maximum likelihood estimator, $D$ is equal to the $-2$ log-likelihood ratio statistic comparing the model under investigation, where the restrictions $\eta_i = g(\mu_i) = \mathbf{b}_i'\boldsymbol{\beta}$ hold, with the unrestricted model with a separate mean for each observation. For binomial counts:

$$D = 2 \sum \{x \log(x/(np)) + (n - x)\log((n - x)/(n - np))\}.$$

Within the exponential family, $Q$ is essentially equal to a log-likelihood ratio, as illustrated by (5) for $\phi = 0$: $L(np; x, n)$ is the log-likelihood of a binomial distribution with probability $p$ and total $n$ (except for some unimportant terms depending on the observations only). By analogy, the quasi-deviance is defined as

$$D_q = -2Q.$$

From expression (5) for the present model:

$$D_q = 2 \sum (1 + \phi(n - 1))^{-1}(x \log(x/(np_0)) + (n - x)\log((n - x)/(n - np_0))).$$

The difference between the deviances of two GLMs, one nested within the other, yields the $-2$ log-likelihood ratio comparing these models. Similarly, the difference between two quasi-deviances yields the quasi-likelihood ratio statistic. The deviance of a GLM is standard output in GENSTAT and for a binomial error distribution with a log link and prior weights $(1 + \phi(n - 1))^{-1}$, GENSTAT will produce $D_q$.

In the terminology of McCullagh (1983) and McCullagh and Nelder (1989), the factor $((1 + \phi(n - 1))$ is included in the variance function $V$.

An alternative is the quasi-Wald test based on approximate normality of the parameter estimators on the logit scale or a quasi-score test based on approximate normality of the quasi-scores [the left-hand sides of (4)]; see Breslow (1990).

### 4.2 *Unknown Dispersion Parameter* $\phi$

Unfortunately $\phi$ is not known. Therefore in the preceding derivation an estimate $\hat{\phi}$ will be used. The estimate is derived by a method of moments based on Pearson's chi-square statistic and suggested by Williams (1982). This is also an iterative procedure obtained by manipulation of the residual sum of squares in the weighted regression for the artificial dependent variable $y$. Details are given in Appendix A.2. The analysis can then be handled with GENSTAT, as shown in Appendix A.3. At convergence, for the estimate $\hat{\phi}$, Pearson's chi-square statistic will be equal to its degrees of freedom $m - q$. Actually (Moore, 1986) we have simply added an extra equation for the estimation of the dispersion parameter $\phi$ to the quasi-likelihood equations (4) for the location parameters $\boldsymbol{\beta}$:

$$\sum_i \{(x_i - n_i p_{0i})^2/((1 + \phi(n_i - 1))n_i p_{0i}(1 - p_{0i})) - (m - q)/m\} = 0. \tag{6}$$

Observe that the expectations of the left-hand sides of (4) and (6) are equal to the right-hand sides when $(m - q)/m$ is replaced by 1 in (6). The term $(m - q)/m$ is a correction for the loss of degrees of freedom due to the estimation of $\boldsymbol{\beta}$. The left-hand sides are estimating functions and more information is given in McCullagh and Nelder (1989, §9.4).

Moore (1986) shows that the estimators $\hat{\boldsymbol{\beta}}$ and $\hat{\phi}$ are consistent ($m \to \infty$) and asymptotically normally distributed. The asymptotic variance–covariance matrix of $\hat{\boldsymbol{\beta}}$ is shown to be the same as the one obtained when $\phi$ is assumed to be known, i.e., it is unaffected by the estimation of $\phi$. This matrix is readily available in GENSTAT. For the present model $\hat{\boldsymbol{\beta}}$ and $\hat{\phi}$ are asymptotically independent. In the analysis the estimate for $\phi$ from the largest model fitted will be used for all subsequent models as well.

## 5. Results

The largest model studied, in an obvious notation for the grand mean, main effects, and interactions, is

$$\text{logit}(p_0) = \mu + T + A + M + N + T.A + T.M + A.M + T.A.M.$$

The estimate for the dispersion parameter is $\hat{\phi} = -.0751$. This suggests that within-ewe competition is present. We will try to substantiate this supposition, i.e., see whether there is evidence to reject the hypothesis $H_0$: $\phi = 0$, by two approaches. The first approach will be based on the asymptotic distribution of $\hat{\phi}$; the second approach will be based on Pearson's chi-square statistic $X^2_P$ under the null hypothesis $H_0$.

The expression for the asymptotic variance of $\hat{\phi}$ given by Moore (1986) depends on the third and fourth central moments, say $\mu_3$ and $\mu_4$, of the distribution of the observations $x$. Since these moments cannot be estimated from the data with any reasonable accuracy, we will resort to a property that holds for the cumulants of distributions in the exponential family: $\kappa_{r+1} = \kappa_2 \partial \kappa_r / \partial \kappa_1$, $r = 1, 2, \ldots$. Assuming that this property approximately holds for the present problem for $r = 2, 3$, the following expressions can be derived from the first two moments in (3):

$$\mu_3 = (1 + \phi(n - 1))^2 np_0(1 - p_0)(1 - 2p_0),$$

$$\mu_4 = (1 + \phi(n - 1))^3 np_0(1 - p_0)(1 - 6p_0(1 - p_0)) + 3(1 + \phi(n - 1))^2 n^2 p_0^2 (1 - p_0)^2.$$

The standard error of $\hat{\phi} = -.0751$ is .075 and with the normal approximation $H_0$ is far from being rejected. However, when the model is reduced to main effects only (we shall see later that it is reasonable to do so), $\hat{\phi} = -.1175$ with standard error .068 and the significance level drops below .10. Because the large-sample approximation may be poor (Moore, 1986), we will also try another approach.

This time we will work under $H_0$: $\phi = 0$ and consider Pearson's $X_P^2$ as a goodness-of-fit statistic, both small and large values being critical. For $\phi = 0$, $X_P^2 = 91.1$, which is less than 102, the corresponding degrees of freedom. To see whether this is significantly less, we need an approximation of the distribution of $X_P^2$ under $\phi = 0$. Although for a large number of units Pearson's statistic will approach the degrees of freedom (McCullagh and Nelder, 1989, §4.5), the conventional approximation by a chi-square distribution is not appropriate because of the relatively small totals $n$. Again we will resort to the exponential family, and this time we will assume that the observations are binomial counts, which is of course only a particular instance of $H_0$. McCullagh (1985, 1986) argues that the appropriate reference distribution for $X_P^2$ is conditional upon the estimates $\hat{\beta}$. In McCullagh and Nelder (1989, §4.4.5), expressions for the conditional mean and variance are given. For the largest model fitted they are 335.7 and 2,933 respectively. With a normal approximation $X_P^2$ falls significantly below its conditional expectation, in agreement with the negative estimate for $\phi$. When the model is reduced to main effects only, $X_P^2 = 93.0$ with 112 degrees of freedom. The conditional mean and variance are 67.2 and 329.9, respectively, and this time the observed value for $X_P^2$ is in agreement with these moments. McCullagh (1985) observes that for low values of the binomial totals $n$, the conditional moments are strongly dependent on the configuration of the data in relation to the model. This seems to be so for this problem as well.

We are now in a tricky position. Evidence that $\phi \neq 0$ is not overwhelming and the estimate $\hat{\phi}$, even when based on main effects only, will probably be very inaccurate. On the other hand, from the physical background of the problem, $\phi \neq 0$ is quite plausible and there does not seem to be any particular reason for letting $\phi$ equal 0, except that test procedures for $\hat{\beta}$ will be more conservative than with a negative value. Since this analysis is mainly exploratory, it was decided to use the estimate $\hat{\phi} = -.0751$ for *all* models fitted. Qualitative conclusions for $\hat{\phi} = -.0751$ from the largest model fitted, $\hat{\phi} = -.1175$ from the main effects model, and $\phi = 0$, with respect to the effects of treatment, age, mating period, and number of ovulations, are found to be similar.

In Table 2 test results for the interaction terms are shown. For example, the test for the two-factor interaction $T.A$ is based on the deviances of the models

$$\mu + T + A + M + N + T.A + T.M + A.M \quad (T.A.M \text{ already dropped from the model})$$

and

$$\mu + T + A + M + N \qquad + T.M + A.M \quad (T.A \text{ also dropped from the model}).$$

These deviances are 104.4 and 105.5, respectively, resulting in QLR = 105.5 − 104.4 = 1.1, as shown in the table. In view of the test results in Table 2, the model is reduced to main effects only:

$$\text{logit}(p_0) = \mu + T + A + M + N.$$

**Table 2**
*Test results for interactions*

| Interaction | Quasi-likelihood ratio QLR | Degrees of freedom | *P*-value |
|---|---|---|---|
| $T.A.M$ | 3.9 | 3 | .27 |
| $T.A$ | 1.1 | 3 | .78 |
| $T.M$ | 2.1 | 1 | .15 |
| $A.M$ | 1.3 | 3 | .73 |

In the reduced model the $P$-values for $T$, $A$, $M$, and $N$ are .06, .14, 1.00, and .07, respectively. We conclude that there is no apparent effect of the mating period $M$. When we concentrate on the contrast between classes 1 and 4 (the youngest versus the oldest animals), a $P$-value of .04 is found for factor $A$. Hence, the age of the ewe may be of importance. Without factor $N$ (for the number of ovulations) in the model, treatment and control are significantly different ($P < .01$). On average, the ratio $x/n$ is decreased by .12 by using Fecundin. A simple test based on rank numbers within combinations of factors $A$ and $M$ of the ratios $x/n$ also gives a highly significant result. This is no proof, but adds considerably to the plausibility of the following statement:

> For ewes treated with Fecundin the embryonic development rate is significantly reduced. However, this is at least partly due to a decrease in the probability for development of higher numbers of ovulations.

When factor $N$ is not in the model, there are no apparent age effects. Possibly two opposing forces are acting:

**(i)** Higher age corresponds to a higher number of ovulations. But for higher numbers of ovulations the probability for development is reduced.
**(ii)** At a fixed number of ovulations, higher age will correspond to a higher probability for development.

Without $N$ in the model, (i) and (ii) largely appear to neutralize each other. Including $N$ in the model makes a correction for (i) and consequently (ii) shows up significantly in the analysis.

Parameter estimates on the logit scale are shown in Table 3. In view of the size of the data set and the standard errors in Table 3, it seems ill advised to draw very detailed (quantitative) conclusions. Reestimation of $\phi$ in the reduced model yields $\hat{\phi} = -.1175$. With this alternative estimate, parameter estimates are similar to the estimates obtained before; $P$-values are slightly reduced and just over .05 for factors $N$ and $T$.

It is inherent in the use of link functions that simplification of the model on the scale of the link function usually does not simplify the presentation of results on the original scale, e.g., no reduction in interaction terms. Often the presentation on the original scale is rather messy. Only a few results on the original scale will be presented. Table 3 gives mean percentages for the various factors on the original scale. These percentages are averages on the original scale; i.e., estimated means on the logit scale are calculated for all combinations of factor levels, then transformed back and averaged on the original, natural scale. They are obtained with the directive PREDICT in GENSTAT 5. Averaging is done with equal weights for the factor combinations. To obtain an indication of the probability of development of a random ovulation for a random ewe corresponding to a particular factor level, weighting with the population proportions would be more appropriate, when reliable estimates for these proportions are available. Using the (unreliable) sample proportions yields the results in the last column of Table 3. Corresponding to the raw means in Table 1, means based on sample proportions

**Table 3**
*Estimates and standard deviations (in parentheses) for grand mean and main effects on the logit scale and estimated means and standard errors on the original scale (in percentages)*

| | | Logit scale | Original scale: Estimated mean percentage | |
|---|---|---|---|---|
| | Parameter | Estimate | Equal weights | Sample proportions as weights |
| Grand mean | $\mu$ | 1.41 (.18) | 79 (3) | 82 (2) |
| Fecundin | $T_1$ | −.33 (.18) | 73 (3) | 75 (3) |
| Control | $T_2$ | .33 (.18) | 84 (4) | 88 (3) |
| Age ⩽.5 | $A_1$ | −.55 (.35) | 69 (9) | 77 (6) |
| Age .5–1.5 | $A_2$ | −.20 (.23) | 76 (4) | 79 (4) |
| Age 1.5–2.5 | $A_3$ | .18 (.28) | 82 (4) | 82 (4) |
| Age ⩾2.5 | $A_4$ | .58 (.29) | 87 (4) | 88 (3) |
| Mating per. Oct. 1 | $M_1$ | −.03 (.15) | 78 (4) | 81 (3) |
| Mating per. Oct. 22 | $M_2$ | .03 (.15) | 79 (4) | 82 (3) |
| Ovulations ⩽2 | $N_1$ | .33 (.18) | 84 (3) | 84 (3) |
| Ovulations ⩾3 | $N_2$ | −.33 (.18) | 73 (5) | 74 (4) |

with respect to factor $N$, i.e., (unweighted) averages of ratios $\hat{\mu}/n$ of fitted values and numbers of ovulations, are shown.

## 6. Discussion

We shall give a brief discussion of some alternatives for the analysis of the model presented.

The moments in (3) are also valid for the beta-binomial model (Crowder, 1978; Williams, 1982). Although derived for a nonnegative correlation $\phi$, the beta-binomial likelihood is also a proper likelihood for negative $\phi$ bounded from below, the lower bound depending on $p_0$ and $n$ and approaching 0 for increasing values of $n$ (Prentice, 1986). A quasi-likelihood approximation to maximum likelihood, to ease the computational burden, is described by Brooks (1984). For $\rho = 0$ and $\phi = \sigma^2 > 0$, the beta-binomial model would be an appealing candidate to fit the assumptions in Section 3, but for $\phi < 0$ the only thing that remains is a likelihood function satisfying the moments in (3).

The moments in (3) also apply to the correlated binomial (CB) model (Kupper and Haseman, 1978; Altham, 1978) and the beta-correlated-binomial (BCB) model (Paul, 1987). In the BCB model, in the notation of the present paper, the contribution $\epsilon$ of the ewe is assumed to follow a beta distribution, while conditional upon the probability $p$, the number of fetuses $x$ is following a CB distribution. In the CB distribution the probability for $x$ fetuses out of $n$ ovulations is equal to the probability under a binomial distribution multiplied by the "correction" factor:

$$1 + \rho((x - np_0)^2 + x(2p_0 - 1) - np_0^2)/(2p_0(1 - p_0)).$$

For a proper likelihood, $\rho$ is bounded from below and above, complicating numerical maximization of the likelihood. Both the lower and upper bounds depend on $p_0$, $\sigma^2$, and $n$.

With the use of quasi-likelihood the choice of a particular likelihood is avoided. Furthermore, because the method is based on iterative weighted least squares, some robustness can be expected, for instance with respect to the assumption that $\sigma^2$ and particularly $\rho$ are independent of the combination of factor levels or the ewe. With the beta-binomial model, when the variance of the beta distribution is incorrectly assumed to be constant over the units, maximum likelihood estimators can be seriously biased (Kupper et al., 1986; Williams, 1988a).

An alternative related approach, also based on the moment assumptions (3) only, is Nelder and Pregibon's (1987) extended quasi-likelihood; see also McCullagh and Nelder (1989, §9.6 and Chap. 10), Davidian and Carroll (1988), Carroll and Ruppert (1988, §§3.3.4, 3.4.4), and Nelder and Lee (1991). The algorithm for extended quasi-likelihood also consists of a combination of two algorithms: the original quasi-likelihood procedure for the location parameters on the logit scale and an algorithm for the dispersion parameter(s), now based on deviance residuals rather than Pearson residuals. Williams' approach was preferred because it ties in nicely with the residual sum of squares in the iterative weighted regression procedure and because Pearson's chi-square generally seems preferable to the deviance for estimation of dispersion parameters when the totals $n$ are relatively small (Williams, 1988b). For other approaches based on residuals see Carroll and Ruppert (1988, e.g. Chap. 3).

Although $\phi$ is expressed as a function of $\rho$ and $\sigma^2$, this is hardly of consequence for the analysis, since only the first two moments in (3) are employed. However, the expression for $\phi$ does show that interpretation of negative or positive values of $\phi$ with respect to internal competition between ovulations is less straightforward than it might seem when (3) is stated directly. Even for $\rho < 0$, with a sizeable value for the between-ewe variance $\sigma^2$, the overall correlation $\phi$ may be positive. In fact, for larger values of $n$ the opportunity for underdispersion becomes more and more remote. Even for positive $\phi$, the possible presence of internal competition indicates that the beta-binomial model is not as intuitively acceptable as it may seem at first sight. Apparently in the BCB model information about $\sigma^2$ and $\rho$ separately is recovered from higher-order moments than the first two. This seems to limit the value of the BCB distribution for practical use; in many cases even the choice of a variance function will be difficult, let alone that estimation critically depends on higher-order moments. When the ewe effect is introduced with constant variance on the logit scale, $\sigma^2$ in (3) has to be replaced by $\sigma^2 p_0(1 - p_0)$. Now the variance is truly dependent on two dispersion parameters. This variance function is not covered by Moore (1986). Similarly to Moore (1987), an extra estimation equation may be added to (4) and (6).

It is hard to find conclusive evidence that $\phi$ is different from 0 when the totals $n$ are relatively small; the large-sample approximation (Moore, 1986) for the distribution of $\hat{\phi}$ depends on the third and fourth central moments and may be poor, McCullagh's (1985, 1986) conditional approach seems to behave rather erratically, and conditional moments are available only for members of the exponential family. A Monte Carlo study, including a study of the distribution of $\hat{\phi}$ and the impact

of the estimation of $\hat{\phi}$ on test results for $\hat{\beta}$, would be of obvious interest and is presently being considered as an object of further research.

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## Résumé

Des observations provenant d'une étude de développement d'ovulations en embryons pour des moutons Texel sont analysées avec un modèle pour données de comptage qui sont moins (ou plus) dispersées par rapport à la variation binomiale. L'analyse est fondée sur le maximum d'une quasi-vraisemblance (McCullagh and Nelder, 1989, *Generalized Linear Models*, 2ème édition, Londres: Chapman et Hall) suivant ainsi une approche suggérée par Williams (1982, *Applied Statistics* **31**, 144–148). On développe le paramètre de dispersion comme combinaison d'une composante de la variance (représentant les effets maternels partagés) et une corrélation, typiquement négative, entre ovulations intra-brebis. Le nombre d'ovulations (le dénominateur de la binomiale) est inclus comme régresseur.

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## APPENDIX

### *A.1 The Data*

Factors $T$ (Treatment; 1: Fecundin; 2: Control), $A$ (Age; 1: ≤.5; . . . ; 4: >2.5 years), $M$ (Mating period; 1: October 1; 2: October 22), variables $n$ (number of ovulations) and $x$ (number of fetuses) per ewe.

| $T$ | $A$ | $M$ | $n$ | $x$ | $T$ | $A$ | $M$ | $n$ | $x$ | $T$ | $A$ | $M$ | $n$ | $x$ | $T$ | $A$ | $M$ | $n$ | $x$ | $T$ | $A$ | $M$ | $n$ | $x$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 4 | 1 | 3 | 2 | 2 | 2 | 1 | 3 | 2 | 2 | 3 | 1 | 3 | 2 |
| 1 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 4 | 1 | 3 | 3 | 2 | 2 | 1 | 2 | 1 | 2 | 3 | 1 | 2 | 2 |
| 1 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 4 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 3 | 2 | 2 | 1 |
| 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 3 | 2 | 1 | 4 | 1 | 3 | 3 | 2 | 2 | 1 | 2 | 1 | 2 | 3 | 2 | 2 | 2 |
| 1 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 4 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 3 | 2 | 2 | 1 |
| 1 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 4 | 2 | 4 | 4 | 2 | 2 | 1 | 2 | 1 | 2 | 3 | 2 | 2 | 2 |
| 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 2 | 1 | 4 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 3 | 2 | 2 | 2 |
| 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 1 | 1 | 4 | 2 | 4 | 3 | 2 | 2 | 1 | 3 | 2 | 2 | 3 | 2 | 2 | 2 |
| 1 | 1 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 2 | 1 | 4 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 4 | 1 | 2 | 1 |
| 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 4 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 4 | 1 | 2 | 2 |
| 1 | 1 | 2 | 2 | 1 | 1 | 3 | 1 | 3 | 3 | 1 | 4 | 2 | 5 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 1 | 2 | 2 |
| 1 | 1 | 2 | 2 | 1 | 1 | 3 | 1 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 1 | 2 | 2 |
| 1 | 1 | 2 | 1 | 1 | 1 | 3 | 1 | 2 | 1 | 2 | 1 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 1 | 2 | 2 |
| 1 | 2 | 1 | 2 | 1 | 1 | 3 | 1 | 3 | 3 | 2 | 1 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 1 | 3 | 3 |
| 1 | 2 | 1 | 2 | 2 | 1 | 3 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 1 | 2 | 2 |
| 1 | 2 | 1 | 2 | 2 | 1 | 3 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 1 | 2 | 2 |
| 1 | 2 | 1 | 4 | 2 | 1 | 3 | 2 | 4 | 4 | 2 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 4 | 2 | 2 | 2 |
| 1 | 2 | 1 | 3 | 2 | 1 | 3 | 2 | 4 | 3 | 2 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 2 | 2 | 2 |
| 1 | 2 | 1 | 2 | 2 | 1 | 3 | 2 | 4 | 1 | 2 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 4 | 2 | 2 | 1 |
| 1 | 2 | 1 | 2 | 2 | 1 | 3 | 2 | 3 | 3 | 2 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 4 | 2 | 2 | 2 |
| 1 | 2 | 1 | 2 | 1 | 1 | 3 | 2 | 3 | 2 | 2 | 1 | 2 | 1 | 1 | 2 | 3 | 1 | 2 | 2 | 2 | 4 | 2 | 2 | 2 |
| 1 | 2 | 1 | 2 | 2 | 1 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 2 | 3 | 1 | 3 | 3 | 2 | 4 | 2 | 3 | 3 |
| 1 | 2 | 1 | 3 | 1 | 1 | 4 | 1 | 3 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 3 | 1 | 2 | 1 | 2 | 4 | 2 | 3 | 3 |
| 1 | 2 | 2 | 2 | 2 | 1 | 4 | 1 | 2 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 3 | 1 | 2 | 2 | | | | | |

### *A.2 Estimation of the Under- or Overdispersion Factor $\phi$*

Let $\phi_*$ be an initial guess for $\phi_0$—for instance, $\phi_* = 0$. Determine an estimate for $\beta$, say $\beta_*$, corresponding to $\phi_*$, with the GLM algorithm. Let $p_*$ correspond to $\beta_*$. The weights $w = 1/(1 + \phi(n - 1))$ for the ewes are collected in a diagonal matrix $\mathbf{W} = \text{diag}(w)$. Similarly, the vectors $\mathbf{b}$ for the ewes are collected in the design matrix $\mathbf{B}$, each row corresponding to a ewe and its vector $\mathbf{b}$. Suppose that $\mathbf{W}_*$ corresponds to $\phi_*$ and $\mathbf{W}_0$ to the true $\phi_0$.

Pearson's chi-square statistic is defined by

$$X^2_P = \sum w_*(x - np_*)^2/(np_*(1 - p_*)),$$

which can be written as the residual sum of squares

$$X^2_P = (\mathbf{Y}_* - \mathbf{B}\beta_*)'\mathbf{W}_*\mathbf{V}_*(\mathbf{Y}_* - \mathbf{B}\beta_*),$$

where $\mathbf{Y}_*$ is the vector of (artificial) dependent variables $y$ corresponding to $\beta_*$ and $\phi_*$ and $\mathbf{V}_* = \text{diag}(v_*)$ with $v_* = np_*(1 - p_*)$. Furthermore,

$$\mathbf{B}\beta_* = \mathbf{Q}_*\mathbf{W}_*\mathbf{V}_*\mathbf{Y}_*, \quad \text{where } \mathbf{Q}_* = \mathbf{B}(\mathbf{B}'\mathbf{W}_*\mathbf{V}_*\mathbf{B})^{-1}\mathbf{B}'.$$

$Q_*$ is the variance–covariance matrix of the estimator for the linear predictor $\hat{\eta} = \mathbf{B}\hat{\beta}$. Ignoring the fact that the elements of $\mathbf{V}_*$ are random variables, it follows (Searle, 1971, p. 55) that

$$\begin{aligned} E(X_P^2) &= E(\text{trace}(X_P^2)) \\ &= \text{trace}\{(\mathbf{I} - \mathbf{Q}_*\mathbf{W}_*\mathbf{V}_*)'\mathbf{W}_*\mathbf{V}_*(\mathbf{I} - \mathbf{Q}_*\mathbf{W}_*\mathbf{V}_*)(\mathbf{W}_0\mathbf{V}_*)^{-1}\} \\ &\quad + \beta_0'\mathbf{B}'(\mathbf{I} - \mathbf{Q}_*\mathbf{W}_*\mathbf{V}_*)'\mathbf{W}_*\mathbf{V}_*(\mathbf{I} - \mathbf{Q}_*\mathbf{W}_*\mathbf{V}_*)\mathbf{B}\beta_0. \end{aligned}$$

Since $\mathbf{W}_*\mathbf{V}_*(\mathbf{I} - \mathbf{Q}_*\mathbf{W}_*\mathbf{V}_*)\mathbf{B} = 0$, the expression above simplifies to

$$\begin{aligned} E(X_P^2) &= \text{trace}\{(\mathbf{I} - \mathbf{Q}_*\mathbf{W}_*\mathbf{V}_*)'\mathbf{W}_*\mathbf{V}_*(\mathbf{I} - \mathbf{Q}_*\mathbf{W}_*\mathbf{V}_*)(\mathbf{W}_*\mathbf{V}_*)^{-1}\mathbf{W}_*\mathbf{W}_0^{-1}\} \\ &= \text{trace}\{(\mathbf{I} - \mathbf{V}_*\mathbf{W}_*\mathbf{Q}_*)\mathbf{W}_*\mathbf{W}_0^{-1}\} = \sum w_*(1 - v_*w_*q_*)/w_0, \end{aligned}$$

where $q_*$ is taken from the diagonal of $\mathbf{Q}_*$. The products $v_*w_*q_*$ are the "leverages." An improved value for $\phi$ may be solved from

$$X_P^2 = \sum w_*(1 - v_*w_*q_*)(1 + (n - 1)\phi).$$

This procedure may be repeated until convergence. At convergence

$$X_P^2 = \text{trace}(\mathbf{I} - \hat{\mathbf{V}}\hat{\mathbf{W}}\hat{\mathbf{Q}}) = m - q,$$

since $\hat{\mathbf{V}}\hat{\mathbf{W}}\hat{\mathbf{Q}}$ is an idempotent matrix. An alternative expression for solving $\phi$ is given by Moore (1987).

*A.3 Some GENSTAT Code*

With the following GENSTAT directives the estimate $\hat{\phi} = -.0751$ is obtained. The algorithm was allowed to run for 20 iterations, which in all cases was enough to obtain convergence. A stop criterion may be included.

```
CALC phi=0                                          Start with φ = 0
FOR run=1 . . . 20                                  20 runs
  CALC w=1/(1+phi*(n-1))                            Prior weights
  MODEL [dist=binomial;link=logit;weight=w] x; nbin=n   Logistic regression with
                                                        prior weights
  FIT [pr=*] T*M*A+N                                Fitting the model and
                                                    saving results from
                                                    the fit
  RKEEP x; leverage=vwq; Pearsonchi=XP2;
  CALC help=w*(1-vwq)                               Calculation of a new
                                                    value for the parameter φ
  CALC phi=(XP2-SUM(help))/SUM((n-1)*help)
  PRINT[ipr=*; sq=y] run,phi,XP2; f=8,(10)2; d=0,4,2   Print the run number,
                                                       φ, and X²_P
ENDFOR
```

The GLM algorithm may be controlled with the RCYCLE directive—for instance, specifying fitted values from an iteration step as starting values for the next one; there was no need for that for the embryo data since the algorithm runs smoothly enough as it is.

The quasi-likelihood ratio test for the interaction *T.A* was calculated as follows:

```
CALC phi=-0.0751 : & w=1/(1+phi*(n-1))
MODEL[dist=binomial;link=logit;weight=w]x ; nbin=n
FIT T+M+A+N+T.M+T.A+M.A
RKEEP x ; deviance=qdev1 ; df=df1
FIT T+M+A+N+T.M+M.A
RKEEP x ; deviance=qdev2 ; df=df2
CALC QLR=qdev2-qdev1 : & df=df2-df1
PRINT QLR, df
```

# Chapter 4

## A simple approach for the analysis of generalized linear mixed models

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A general discussion of estimation by IRREML in GLMMs.

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# A simple approach for the analysis of generalized linear mixed models

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A broad class of generalized linear mixed models, e.g. variance components models for binary data, percentages or count data, will be introduced by incorporating additional random effects into the linear predictor of a generalized linear model structure. Parameters are estimated by a combination of quasi-likelihood and iterated MINQUE (minimum norm quadratic unbiased estimation), the latter being numerically equivalent to REML (restricted, or residual, maximum likelihood). First, conditional upon the additional random effects, observations on a working variable and weights are derived by quasi-likelihood, using iteratively re-weighted least squares. Second, a linear mixed model is fitted to the working variable, employing the weights for the residual error terms, by iterated MINQUE. The latter may be regarded as a least squares procedure applied to squared and product terms of error contrasts derived from the working variable. No full distributional assumptions are needed for estimation. The model may be fitted with standardly available software for weighted regression and REML.

*Key words & Phrases:* GLMM, categorical data, GLM, components of variance, overdispersion, quasi-likelihood, pseudo-likelihood, REML, MINQUE.

## 1 Introduction

A linear model (LM)

$$y = \mu + \varepsilon, \qquad \mu = X\beta,$$

is a useful tool for the analysis of continuous independently distributed observations with variances independent of the means. In a LM the linear predictor $X\beta$ is equal to the vector of means $\mu$. For statistical inference the residual error terms $\varepsilon$ are usually assumed to be normally distributed with mean 0 and constant variance $\sigma^2$.

A LM may be extended to a generalized linear model (GLM) (McCullagh and Nelder, 1989). In a GLM the mean $\mu$ is related to a linear predictor $\eta$ by means of a known link function $g$:

$$g(\mu) = \eta = X\beta.$$

In a factorial experiment for binomial data with totals $n$ and probabilities $\pi$ for instance, main effects and interactions may be introduced on a logit scale:

$$\text{logit}\left(\frac{\mu}{n}\right) = \text{logit}(\pi) = \log\left(\frac{\pi}{1-\pi}\right) = X\beta.$$

This makes more sense than modelling on the original scale, where means $\mu$ are restricted to the interval $(0;n)$. For Poisson data, where $\mu$ is restricted to be positive, a multiplicative model is often appropriate and a logarithmic link function can be used.

The distribution of the error terms $\varepsilon$ is from an exponential family, including the binomial, Poisson and normal distribution. Parameters in $\beta$ may be estimated by maximum likelihood. In a GLM the variance of the observations is completely determined by the mean, possibly except for a multiplicative constant $\phi$, called the dispersion factor:

$$\text{Var}(y) = \phi V(\mu).$$

For the binomial and the Poisson distribution $\phi = 1$. When no full distributional assumptions are made and only the relationship between the variance and the mean is specified, parameters may be estimated by maximum quasi-likelihood (QL) (McCULLAGH and NELDER, 1989, Ch. 9).

Two important properties of a LM are relaxed: the linear predictor is introduced on the link scale and variances may depend on the means. The assumption of independence between observations is retained.

Another important extension of a LM is the linear mixed model (LMM) (ENGEL, B., 1990), which allows the incorporation of additional random effects:

$$y = \mu + Zu + \varepsilon, \qquad \mu = X\beta,$$

where $u$ is a vector of additional random effects with design matrix $Z$. LMM's are useful for the analysis of (positively) correlated observations. For statistical inference, elements of $u$ and $\varepsilon$ are usually assumed to be independently normally distributed. Often, when $u$ corresponds to $c$ sources of additional random variation, the covariance matrix of $u$ is of a block diagonal form:

$$\text{Var}(u) = \text{diag}(A_i \sigma_i^2) \quad \text{and} \quad \text{Var}(\varepsilon) = A_0 \sigma_0^2,$$

where in many applications the known matrices $A_i$ $(i = 0 \ldots c)$ are equal to identity matrices. A well known example of a LMM is the split plot model, where correlation between observations on the same whole plot, e.g. a plot, batch, animal or plant, is represented by a common whole plot "error" $u$. In the split plot model there are two components of variance: $\sigma_0^2$, representing (residual) variation within whole plots and $\sigma_1^2$, representing variation between whole plots that is not "explained" by the residual variation.

In a LMM only the assumption of independence is relaxed: observations with common random terms are positively correlated. Linearity still pertains to the scale of the observations and variances and covariances are independent of the means.

In a number of practical situations both GLM and LMM extensions are needed simultaneously, e.g. a split plot design for binomial count data with a factorial structure,

introducing main effects and interactions on a logit scale. In the spirit of a GLM, a class of generalized linear mixed models (GLMM) will be introduced by adding random effects to the linear predictor $\eta$ on the link scale, i.e. on the link scale a LMM structure is assumed.

As an example consider the following experiment where different diluents for boar-semen are compared with respect to motility of spermatozoa. Semen, used in artificial insemination of pigs, was diluted with six different diluents. For each diluent 18 bottles are prepared and placed in storage at 18 °C. On six successive days, each day from three bottles test tubes are taken. After heating to 37 °C two samples of spermatozoa are taken from each test tube. To one sample caffein was added. Caffein possibly reduces the time needed to bring spermatozoa to their maximal motility. The fraction of normally moving spermatozoa $y$ was determined for each sample. Shared effects within bottles and tubes may be represented by a random effect $u_1$ with variance $\sigma_1^2$ on the logit scale for the probability of normal movement $\mu$. Assuming variation between samples from the same test tube to be a multiple of the binomial variance function, conditional upon $u_1$, i.e. for a particular bottle and tube:

$$E(y \mid u_1) = \mu, \quad \text{Var}(y \mid u_1) = \phi\mu(1-\mu) \quad \text{and} \quad \text{logit}(\mu) = x'\beta + u_1,$$

where $x'\beta$ represents the effects of diluents, time of storage (days) and caffein on the logit scale and

$$E(u_1) = 0, \quad \text{Var}(u_1) = \sigma_1^2.$$

The variance function may be obtained as follows. Suppose that a sample contains $n$ spermatozoa. Conditional upon bottles and tubes within bottles, assume that correlation between binary data (1 = normal movement, 0 = otherwise) for individual spermatozoa is constant and equal to $\phi$. Then the conditional variance follows for $n \to \infty$. Observe that, since $\phi > -1/(n-1)$, in the limit $\phi \geq 0$. Alternatively, and in line with the introduction of the bottle and test tube effects on the logit scale, we may assume that correlation within a sample is constant and equal to $\phi$ on the logit scale. This is equivalent to the introduction of a second uncorrelated random effect with variance $\phi$ on the logit scale. We now have approximately:

$$E(y \mid u_1) = \mu, \quad \text{Var}(y \mid u_1) = \phi\mu^2(1-\mu)^2 \quad \text{and} \quad \text{logit}(\mu) = x'\beta + u_1.$$

In both models bottles and tubes are explicitly introduced as a source of correlation through the random effects $u_1$. Marginal means and (co)variances follow implicitly from the model assumptions. Both models may be analyzed with the estimation procedure presented in this paper.

The GLMM has been discussed by a number of authors, including ANDERSON and HINDE (1988), PREISLER (1988), IM and GIANOLA (1988) and JANSEN (1990, 1992). The method of estimation suggested by these authors is maximum likelihood, assuming normality for the random effects. However, since the random effects have to be integrated "out" to obtain the likelihood, this involves cumbersome numerical integration, e.g. Gauss-Hermite quadrature (ABRAMOWITZ and STEGUN, 1965, p. 924), with severe

limitations on the number and structure of random effects in the linear predictor. Numerical problems with two crossed random effects are already insurmountable.

The Gibbs sampler has been suggested as a Bayesian alternative to maximum likelihood, e.g. ZEGER and KARIM (1991), to relieve some of the computational limitations. This is a Monte Carlo method for generating observations from a complex joint posterior distribution, when sampling from the conditional distributions is easier. It involves a choice of prior distributions for fixed effects and components of variance and rejection sampling to avoid integration problems similar to those encountered with maximum likelihood. Because of the vast amount of computation involved and tricky theoretical and numerical aspects, such as choice of priors, correlation between simulated values, choice of stopping criteria and efficiency of rejection sampling, the Gibbs sampler is not an obvious candidate for a general and practical approach to estimation in GLMM's (yet).

The GLMM is a subject-specific (SS) model: modelling is in terms of subjects or individuals, rather than in terms of the population as a whole. In the latter case models are referred to as population-averaged (PA) models (ZEGER, LIANG and ALBERT, 1988). PA models concentrate on parameters characterizing the marginal distribution of the observations only. In SS models sources of covariance are explicitly introduced through the random effects, implicitly defining a highly structured covariance matrix for the observations. In PA models the covariance matrix must be positive definite, but is, in principle, unrestricted otherwise. SS models obviously are of particular importance in those fields of application where random effects have a direct physical interpretation and the components of variance and/or predictions for random effects are of primary interest, e.g. animal breeding where random effects refer to familial resemblance due to segregation of (many) genes.

In ZEGER, LIANG and ALBERT (1988) a set of generalized estimation equations (GEE) is presented for GLMM models for longitudinal data. The GEE is obtained by extending the geometrical interpretation of least squares: residuals are required to be orthogonal to the tangent space for the mean with respect to the inner product induced by a covariance matrix, along the same lines as for QL (MCCULLAGH, 1991). The GEE is based on an approximate PA model derived from a SS model. Estimates for parameters in the marginal means of the observations are solved from the GEE. The dispersion factor and components of variance are clearly regarded as nuisance parameters and moment estimates are obtained from additional estimating equations. This is an important difference with the estimation procedure proposed in this paper, which is intimately related to the SS nature of the GLMM model and estimates the parameters on the link scale, making use of the working variable in the iterated re-weighted least squares (IRLS) algorithm originally proposed for GLM's (NELDER and WEDDERBURN, 1972) and later on also for QL estimation (WEDDERBURN, 1974).

The mean and covariance matrix of the working variable are approximately of the same structure as in a LMM, with weights in the residual error stratum. Therefore many of the results for LMM's carry over to GLMM's. Taking advantage of efficient numerical methods derived for LMM's, estimation by the estimation procedure proposed in

this paper is straightforward, utilizing standardly available software only. The procedure is a combination of QL and iterated MINQUE (RAO, 1973), the last procedure being equivalent to REML (PATTERSON and THOMPSON, 1971), when estimates for the components of variance are positive. Facilities for QL and REML are available in Genstat 5 (Genstat 5 committee, 1987, 1990), which is the statistical package used in this paper. Basically the estimation procedure is a combination of several iterated least squares procedures and no full distributional assumptions are needed.

In SCHALL (1991) two estimation procedures for a GLMM are derived, purely by mimicking the EM algorithm for maximum likelihood and for REML for an ordinary LMM (see ENGEL, B., 1990) for the IRLS working variable. BRESLOW and CLAYTON (1991) present a penalized quasi-likelihood method (PQL) for a GLMM, which can also be formulated in terms of the IRLS working variable. Both Schall's REML type algorithm and Breslow and Clayton's PQL approach may be expected to produce results similar to those obtained with the method proposed in this paper. They are briefly discussed in §6.

The outline of the paper is as follows. First GLM's and LMM's will be considered in more detail in the next section. Then in §3 the class of GLMM's will be introduced. The estimation procedure will be discussed in §4. In §5 this procedure will be compared with other estimation procedures by re-analysing a number of data sets from the literature. Conclusions will be summarized in §6.

## 2 GLM's and LMM's

*GLM's*

A GLM may be fitted by iteratively re-weighted least squares (IRLS) (NELDER and WEDDERBURN, 1972). A linearization of the mean $\mu$ around an a priori value $\beta_*$ for $\beta$:

$$\mu_j \approx \mu_{*j} + \left(\frac{\partial \mu_j}{\partial \beta}\right)'_{\beta_*} (\beta - \beta_*) = \mu_{*j} + \left(\frac{\partial \mu_j}{\partial \eta_j}\right)_{\beta_*} \left(\frac{\partial \eta_j}{\partial \beta}\right)'_{\beta_*} (\beta - \beta_*)$$
$$= \mu_{*j} + \frac{x_j'(\beta - \beta_*)}{g'(\mu_{*j})} = \mu_{*j} + \frac{g(\mu_j) - g(\mu_{*j})}{g'(\mu_{*j})},$$

motivates the following working variable:

$$\zeta_j = (y_j - \mu_{*j}) g'(\mu_{*j}) + g(\mu_{*j}),$$

where $x_j'$ is the $j$-th row of the design matrix $X$, corresponding to the $j$-th observation $y_j$ with mean $\mu_j$, $j = 1 \ldots N$. Now, to first order:

$$E(\zeta_j) \approx x_j' \beta, \quad \mathrm{Var}(\zeta_j) \approx \phi (g'(\mu_{*j}))^2 V(\mu_{*j}),$$

and $\beta_*$ may be improved by weighted least squares on $\zeta$. Repeated use of weighted least squares solves the equations:

$$\sum_{j=1}^{N} \frac{(y_j - \mu_j)}{V(\mu_j) g'(\mu_j)} x_{jk} = 0, \qquad k = 1 \ldots p,$$

where $x_{jk}$ is the $k$-th element of $x_j$ and $p$ is the number of elements of $\beta$. Within the GLM framework these are the maximum likelihood equations obtained by putting the first derivatives of the log likelihood equal to 0. More general, when no full distributional assumptions are made and only the relationship between variances and means is specified, these are the quasi-likelihood equations defining the quasi-likelihood $Q$ (WEDDERBURN, 1974) as a primitive of the left hand sides:

$$Q = \sum_{j=1}^{N} \int_{y_j}^{\mu_j} \frac{(y_j - t)}{V(t)} \, dt.$$

For details see MCCULLAGH (1983, 1991) and MCCULLAGH and NELDER (1989, ch. 9). When $V(\mu)$ happens to fit within the GLM frame work, e.g.

$$V(\mu) = \frac{\mu(n-\mu)}{n}, \qquad V(\mu) = \mu^{\alpha}, \qquad \alpha = 1, 2, 3,$$

which are variance functions for binomial, Poisson, gamma and inverse Gaussian distributions, quasi-likelihood and maximum likelihood (for these distributions) will yield the same results.

*LMM's*

Consider the linear mixed model

$$y = \mu + Zu + \varepsilon = X\beta + \sum_{i=0}^{c} Z_i u_i, \quad Z_0 = I_N, \quad u_0 = \varepsilon,$$

$$u = (u_1' \ldots u_c')', \quad E(u_i) = 0, \quad \mathrm{Var}(u_i) = A_i \sigma_i^2, \quad i = 0 \ldots c,$$

$u_0, u_1 \ldots u_c$ independent.

Minimum norm quadratic unbiased estimation (MINQUE) was proposed by RAO (1973) as an estimation procedure for the components of variance of a LMM. MINQUE may be derived as a generalized least squares procedure in the dispersion-mean model (SEARLE, 1979; see also VERDOOREN, 1980). From $N - p$ linearly independent error contrasts (linear combinations of the observations with mean 0) collected in, say, $Ky$, squares and products are formed. These are the elements of the matrix $Kyy'K'$. The elements on and below the diagonal are stacked in a vector $s$. The expectation of $s$ is

$$E(s) = F\sigma^2,$$

where $F$ is a known matrix and the elements of the vector $\sigma^2$ are the unknown components of variance: $\sigma^2 = (\sigma_0^2, \sigma_1^2, \ldots \sigma_c^2)'$. Generalized least squares on $s$, with prior values for the components of variance to evaluate $\mathrm{Var}(s)$, yields MINQUE. Iterative generalized least squares, prior values becoming starting values, yields iterated MINQUE. The iterated MINQUE estimates satisfy the following equations:

$$y'PZ_iA_iZ_i'Py = \mathrm{trace}(Z_i'PZ_iA_i), \qquad i = 0 \ldots c,$$

where

$$P = V^{-1} - V^{-1}X(X'V^{-1}X)^{-1}X'V^{-1},$$

$$V = \mathrm{Var}(y) = \sum_{i=0}^{c} Z_i A_i Z_i' \sigma_i^2.$$

The same set of equations is obtained when, under normality, the derivatives of the likelihood of $Ky$ are put equal to 0, yielding REML estimates. Hence, when the estimates for the components of variance are positive, iterated MINQUE and REML yield the same results. In this paper a Fisher scoring algorithm for REML, implemented in Genstat 5, was used.

## 3 Formulation of the generalized linear mixed model (GLMM)

*The basic model*

Conditional upon the random vector $u = (u_1' \dots u_c')'$, observations $y_j$, $j = 1 \dots N$, are independent with conditional means $\mu_j$ and variances $V(\mu_j)$, where $V(\cdot)$ is a known function. The known link function $g$ transforms the conditional expectations to a linear scale:

$$g(\mu_j) = \eta_j = x_j'\beta + z_j'u,$$

where $x_j'$ and $z_j'$ are known vectors of length $p$ and $q$ respectively, the $j$-th rows of design matrices $X$ and $Z$ for fixed effects and random effects in the linear predictor. The elements of the $q_i x 1$ vectors $u_i$, $i = 1 \dots c$, are uncorrelated and

$$E(u_i) = 0, \quad \mathrm{Var}(u_i) = \sigma_i^2 I_{q_i}.$$

The total number of random effects is $q = \sum_{i=1}^{c} q_i$. Suppose that $Z$ is partitioned in correspondence with $u = (u_1' \dots u_c')'$: $Z = (Z_1 \dots Z_c)$ and let $G = \mathrm{Var}(u) = \mathrm{diag}(\sigma_i^2 I_{q_i})$.

*Extension of the model*

$V(\mu)$ may be replaced by $V(\mu, \phi)$, where $\phi$ is an additional unknown dispersion parameter. Unless $\phi$ is a simple multiplicative constant, i.e. $V(\mu, \phi) = \phi V(\mu)$, the estimation procedure presented in §4 has to be modified, as will be discussed later on.

*Moments on the original scale*

It is assumed that third and higher order moments of $u_1 \dots u_c$ are of order $\sigma_i^3$, or for symmetric distributions of order $\sigma_i^4$. Suppose that $\tau = (\tau_1 \dots \tau_N)'$ denotes the vector of means and $D = (d_{jj'})$ the covariance matrix of the observations $(y_1 \dots y_N)'$ on the original scale, i.e. marginal moments, integrating out the random effects $u$.

The dependence of the conditional mean $\mu$ on the random effects $u$ will be denoted as $\mu(u)$. $\tau$ and $D$ will be approximated for small $\sigma_i^2$. Now:

$$\mu_j(u) = \mu_j(0) + \left(\frac{\partial \mu_j}{\partial u}\right)_0' u + \tfrac{1}{2} u' \left(\frac{\partial^2 \mu_j}{\partial u \, \partial u'}\right)_0 u + O_p(\sigma^3),$$

where $O_p(\sigma^3)$ is short for $O_p(\max(\sigma_i^3))$. So

$$\tau_j = \mu_j(0) + \tfrac{1}{2}\,\text{trace}\left(\left(\frac{\partial^2 \mu_j}{\partial u\,\partial u'}\right)_0 G\right) + O(\sigma^3).$$

Furthermore

$$\left(\frac{\partial^2 \mu_j}{\partial u\,\partial u'}\right)_0 = \left(\frac{\partial^2 \mu_j}{\partial \mu_j^2}\right)_0 z_j z_j' = h''(x_j'\beta) z_j z_j',$$

where function $h$ denotes the inverse of the link function $g$, i.e. $\mu_j = h(\eta_j)$. Consequently:

$$\tau_j = \mu_j(0) + \tfrac{1}{2} h''(x_j'\beta) z_j' G z_j + O(\sigma^3).$$

Often the elements of $z_j$ will be 0 or 1 and:

$$\tau_j = \mu_j(0) + \tfrac{1}{2} h''(x_j'\beta) \sum_{i=1}^{c} \sigma_i^2 + O(\sigma^3). \tag{1}$$

Before we proceed to the evaluation of covariance matrix $D$, let's have a look at an example:

*Example:* $g(\mu) = \log(\mu)$, $c = 1$, e.g. a split plot experiment with a multiplicative structure for the treatment effects.

$h(\eta) = e^{\eta}$, $h''(x_j'\beta) = e^{x_j'\beta} = \mu_j(0)$,

$G = I\sigma_1^2$, $z_j' G z_j = \sigma_1^2$. Hence

$\tau_j \approx e^{x_j'\beta}(1 + \tfrac{1}{2}\sigma_1^2)$ and $\log(\tau_j) \approx \tfrac{1}{2}\sigma_1^2 + x_j'\beta$.

To simplify the notation, $V(\mu(u))$ is denoted as $V(u) = \text{diag}(v_j(u))$. Now:

$$D = E_u(V(u)) + \text{Var}_u(\mu(u)). \tag{2}$$

First we tackle the expectation on the right hand side of (2).

$$v_j(u) = v_j(0) + \left(\frac{\partial v_j}{\partial u}\right)_0' u + \tfrac{1}{2} u' \left(\frac{\partial^2 v_j}{\partial u\,\partial u'}\right)_0 u + O_p(\sigma^3),$$

$$E(v_j(u)) = v_j(0) + \tfrac{1}{2}\,\text{trace}\left(\left(\frac{\partial^2 v_j}{\partial u\,\partial u'}\right)_0 G\right) + O(\sigma^3) \quad \text{and}$$

$$\left(\frac{\partial^2 v_j}{\partial u\,\partial u'}\right)_0 = \{v_j''(0) h'(x_j'\beta)^2 + v_j'(0) h''(x_j'\beta)\} z_j z_j',$$

where $v_j'(0)$ and $v_j''(0)$ are derivatives with respect to $\mu_j$ evaluated for $u = 0$, i.e. $\mu_j = x_j'\beta$. Now for the variance of the right hand side of (2):

$$\text{Cov}_u(\mu_j(u), \mu_{j'}(u)) = \left(\frac{\partial \mu_j}{\partial u}\right)_0' G \left(\frac{\partial \mu_{j'}}{\partial u}\right)_0 + O(\sigma^3) \quad \text{and} \quad \left(\frac{\partial \mu_j}{\partial u}\right)_0 = h'(x_j'\beta) z_j.$$

Piecing it all together:

$$d_{jj} = v_j(0) + \tfrac{1}{2}\{v_j''(0)h'(x_j'\beta)^2 + v_j'(0)h''(x_j'\beta) + 2h'(x_j'\beta)^2\}z_j'Gz_j + O(\sigma^3),$$
$$d_{jj'} = h'(x_j'\beta)h'(x_{j'}'\beta)z_j'Gz_{j'} + O(\sigma^3), \qquad j \neq j'. \tag{3}$$

Often, $z_j'Gz_j = \sum_{i=1}^{c}\sigma_i^2$, while $z_j'Gz_{j'}$ is a sum of a subset of $\sigma_1^2 \ldots \sigma_c^2$ representing a covariance on the link scale.

*Example (continued):* let $V(\mu) = \mu$, e.g. Poisson data.

$h'(x_j'\beta) = h''(x_j'\beta) = e^{x_j'\beta} = v_j(0), \quad v_j'(0) = 1, \quad v_j''(0) = 0.$ Now

$d_{jj} \approx e^{x_j'\beta} + \tfrac{1}{2}\{e^{x_j'\beta} + 2e^{2x_j'\beta}\}\sigma_1^2$ and

$d_{jj'} \approx \sigma_1^2 e^{x_j'\beta + x_{j'}'\beta}, \quad j \neq j',$

when $y_j$ and $y_{j'}$ have one of the random effects in common, 0 otherwise. Hence, ignoring terms of order $\sigma_1^4$:

$$d_{jj} \approx \tau_j + \sigma_1^2\tau_j^2,$$
$$d_{jj'} \approx \sigma_1^2\tau_j\tau_{j'} \quad \text{or} \quad 0, \quad j \neq j'.$$

Expressions (1) and (3) may give an impression of the impact of the parameters, the components of variance in particular, on the original scale. The example illustrates that a SS model can motivate the choice of a particular, highly structured, PA model, although the latter model will not always show such agreeable features as in this case. In general, inference and interpretation of results for the estimation procedure proposed in the next section will be mainly restricted to the link-scale. Results on the original scale may be obtained from back-transformation by $h(\cdot) = g^{-1}(\cdot)$, correcting, up to first order, for the components of variance.

## 4 Estimation

*The basic algorithm*

Estimation proceeds in two steps.

Step 1 (GLM step):

(i) Conditional upon $u$, the expectations $\mu_j, j = 1 \ldots N$, are estimated by QL; or equivalently, when the conditional distribution fits within the GLM frame-work, by maximum likelihood. The estimates will satisfy the following equations:

$$\sum_{j=1}^{N}\left(\frac{y_j - \mu_j}{V(\mu_j)g'(\mu_j)}\right)x_{jk} = 0, \qquad k = 1 \ldots p,$$
$$\sum_{j=1}^{N}\left(\frac{y_j - \mu_j}{V(\mu_j)g'(\mu_j)}\right)z_{jm} = 0, \qquad m = 1 \ldots q, \tag{4}$$
$$g(\mu_j) = \sum_{k=1}^{p} x_{jk}\beta_k + \sum_{m=1}^{q} z_{jm}u_m, \qquad j = 1 \ldots N,$$

where $x_{jk}$ and $z_{jm}$ are elements of vectors $x_j$ and $z_j$ respectively. Although there

may not exist a unique solution for $\beta_k$, $k = 1 \ldots p$ and $u_m$, $m = 1 \ldots q$, we will assume that the solution for $\mu_j$, $j = 1 \ldots N$, is unique. The equations may be solved by iterated least squares on a working variate

$$\zeta_j^{(l+1)} = (y_j - \mu_j^{(l)})g'(\mu_j^{(l)}) + g(\mu_j^{(l)}),$$

where $\mu_j^{(l)}$ denotes the current value for $\mu_j$ and $\mu_j^{(l+1)}$ is obtained from weighted least squares on $\zeta^{(l+1)}$. For the final estimates $\hat{\mu}_j$:

$$\zeta_j = \zeta_j^{(\infty)} = (y_j - \hat{\mu}_j)g'(\hat{\mu}_j) + g(\hat{\mu}_j).$$

For $\zeta = (\zeta_1 \ldots \zeta_N)'$, $g(\mu) = (g(\mu_1) \ldots g(\mu_N))'$ and $V(\mu) = \text{diag}\,(V(\mu_j))$, to first order:

$$E(\zeta \mid u) \approx g(\mu), \qquad \text{Var}\,(\zeta \mid u) \approx \text{diag}\,(g'(\mu)^2)V(\mu).$$

Step 2 (LMM step):

(ii) Now the $u_i$ will be returned to their proper status as random effects.

$$E(\zeta) = E_u(E(\zeta \mid u) \approx E_u(g(\mu)) = X\beta$$

$$\text{Var}\,(\zeta) = E_u(\text{Var}\,(\zeta \mid u)) + \text{Var}\,(E_u(\zeta \mid u)) \approx E_u(\text{diag}\,(g'(\mu)^2)V(\mu)) + ZGZ'.$$

(iii) An estimate is needed, possibly up to an unknown constant $\sigma_0^2$, of the diagonal matrix

$$E_u(\text{diag}\,(g'(\mu)^2)V(\mu)) = \sigma_0^2 W^{-1} = \sigma_0^2\,\text{diag}\,(w_j^{-1}).$$

For the moment suppose that we have acceptable estimates $\hat{w}_j$. Later on it will be discussed how these estimates may be obtained. We now have

$$E(\zeta) \approx X\beta, \quad \text{Var}\,(\zeta) \approx ZGZ' + \hat{W}^{-1}\sigma_0^2,$$

which is the structure of an ordinary LMM with weights $\hat{W}$ for the residual stratum.

(iv) Estimates for the variance components $\sigma_0^2, \sigma_1^2 \ldots \sigma_c^2$ are obtained by iterated MINQUE, which is yet another iterated weighted least squares procedure, but now applied to squared and product terms of error contrasts obtained from $\zeta$. Fisher scoring as implemented in Genstat 5, with special features for REML, was used to obtain estimates for the components of variance. The following set of equations will be solved for $\sigma_0^2, \sigma_1^2 \ldots \sigma_c^2$:

$$\zeta' P Z_i Z_i' P \zeta = \text{trace}\,(Z_i' P Z_i), \qquad i = 0 \ldots c, \tag{5}$$

with

$$P = \Omega^{-1} - \Omega^{-1}X(X'\Omega^{-1}X)^{-1}X'\Omega^{-1},$$

$$\Omega = ZGZ' + \hat{W}^{-1}\sigma_0^2 = \sum_{i=1}^{c} \sigma_i^2 Z_i Z_i' + \hat{W}^{-1}\sigma_0^2.$$

Estimates for fixed effects $\beta$ may be obtained from generalized least squares:

$$\hat{\beta} = (X'\hat{\Omega}^{-1}X)^{-1}X'\hat{\Omega}^{-1}\zeta, \tag{6}$$

predictions, say $\hat{u}$, for random effects may be obtained from regression, similar to best linear unbiased prediction (BLUP) in a LMM:

$$\hat{u} = \hat{G}Z'\hat{\Omega}^{-1}(\zeta - X\hat{\beta}), \tag{7}$$

where $\hat{\Omega}$ and $\hat{G}$ denote $\Omega$ and $G$ evaluated at the estimates $\hat{\sigma}_0^2 \ldots \hat{\sigma}_c^2$. Estimates $\hat{\beta}$ and predictions $\hat{u}$ may be shown to satisfy the mixed model equations:

$$\begin{pmatrix} X'\hat{W}X & X'\hat{W}Z \\ Z'\hat{W}X & Z'\hat{W}Z + \sigma_0^2\hat{G}^{-1} \end{pmatrix} \begin{pmatrix} \beta \\ u \end{pmatrix} = \begin{pmatrix} X'\hat{W}\zeta \\ Z'\hat{W}\zeta \end{pmatrix} \tag{8}$$

or in terms of the original observations:

$$X'\hat{W}\,\mathrm{diag}\,(g'(\hat{\mu}))(y - \hat{\mu}) = X'\hat{W}(g(\mu) - g(\hat{\mu})) \text{ and} \tag{9}$$

$$Z'\hat{W}\,\mathrm{diag}\,(g'(\hat{\mu}))(y - \hat{\mu}) = Z'\hat{W}(g(\mu) - g(\hat{\mu})) + \sigma_0^2\hat{G}^{-1}u,$$

where $\hat{\mu}$ is from step 1.

Observe that when the link function is the identity, such as is the case in the classical mixed model for normally distributed observations, step (1) simply reproduces the original data: $\zeta = y$. In the classical mixed model: $V(\cdot) \equiv 1$ and $W = I$, step 2 is simply REML on the original observations.

Equations (4), (5) and (6) are the estimating equations for steps 1 and 2 of the estimating procedure. Since REML is based on a normal likelihood for the error contrasts, the estimation procedure shows some similarity to pseudo-likelihood for independent data (CARROLL and RUPPERT, 1988, Ch. 3).

*Extending the basic algorithm*

Step 1 of the algorithm, in some instances, may be rather inefficient. For instance, for an observation with a contribution of a random effect which appears only once in the data, $\zeta$ will be equal to $g(y)$. In such cases step 1 may have to be modified. For example, suppose that offspring of dams are observed, with dam as a random effect, then for offspring of litters with littersize 1, observations should not be analysed conditional upon the dam effect in step 1, i.e. the dam stratum should be pooled with the lowest stratum in the analysis. It is rather tempting to add some extra steps to the estimation procedure, employing the results from step 2, such as:

Step 3a: Update the variable $\zeta$ and weights $w$ and repeat step 2. A prediction of $u$ is needed and an obvious candidate is $\hat{u}$ from (7). We can go even further;

Step 3b: Repeat step 2, updating $\zeta$ and $w$ each time, until convergence. To reduce the computational load, iterated MINQUE may be replaced by ordinary MINQUE, which actually corresponds with one step of the Fisher-scoring algorithm for REML.

With steps 1, 2 and 3b, steps 1 and 2 merely serve to generate proper starting values for step 3b. Addition of 3b is intuitively attractive and often computationally feasible. Any

theoretical justification of 1, 2 and 3b will be asymptotic and will probably also cover the combinations of steps 1, 2, 3a and of steps 1, 2. Whether there is any practical gain in 1, 2, 3b or 1, 2, 3a over 1, 2 is not clear yet.

*Modification of the basic algorithm for extended variance functions*

For the extended model, step 2 may have to be modified for the variance function $V(\mu, \phi)$. The variance function $\phi V(\mu)$ offers no special problems since it has no bearing on $W$. The scale parameter $\phi$ will be equal to, or part of, the residual component $\sigma_6^2$.

For the more general variance function $V(\mu, \phi)$ several approaches are suggested in the literature for estimation of $\phi$. WILLIAMS (1982) suggests a method of moments (MM) where $\hat{\phi}$ is obtained by equating Pearson's chi-square to its degrees of freedom, see also MOORE (1986, 1987) and MOORE and TSIATIS (1991). Another, deviance orientated, approach, is extended quasi-likelihood (EQL) (NELDER and PREGIBON, 1987; MCCULLAGH and NELDER, 1989, §9.6 and Ch. 10.). Pseudo-likelihood (PL) is yet another method which relates both to MM and EQL. For a discussion of PL and EQL see DAVIDIAN and CAROLL (1988) and NELDER and LEE (1991, 1992).

Before we proceed to the estimation of $W$ we will briefly look at a few examples of "extended" variance functions (for convenience dropping indices $j$ referring to the observations):

*Examples:*

(i) $V(\mu, \phi) = \mu + \phi\mu^2$,

this is a popular variance function for overdispersed Poisson data (BRESLOW, 1984, 1989, 1990). It is the variance of a negative binomial distribution and may be obtained by sampling the Poisson parameter from a gamma distribution. Ignoring higher order terms, it may also be obtained by adding independent error terms, with mean 0 and variance $\phi$, to the individual observations on the log scale.

(ii) $V(\mu, \phi) = \mu\left(1 - \frac{\mu}{n}\right)(1 + \phi(n-1))$,

this is an example of a variance function for overdispersed binomial data, it is the variance of a beta-binomial distribution (CROWDER, 1978; WILLIAMS, 1982, 1988; PRENTICE, 1986; KUPPER et al., 1986) and correlated binomial distribution (KUPPER and HASEMAN, 1978; ALTHAM, 1978) and relates to the correlated beta-binomial distribution (PAUL, 1987). For a practical example and some discussion see ENGEL and TE BRAKE (1992). By adding independent errors to the individual probabilities on the logit scale, again with mean 0 and variance $\phi$, ignoring higher order terms, the variance function

$$V(\mu, \phi) = \mu\left(1 - \frac{\mu}{n}\right)\left(1 + \phi\left(\frac{n-1}{n}\right)\mu\left(1 - \frac{\mu}{n}\right)\right) \tag{10}$$

is obtained.

When the basic algorithm is extended, parameter $\phi$ in the extended variance function should be updated as well. For instance, for steps 1, 2 and 3b, by equating Pearson's

chi-square to its degrees of freedom, after each repetition of 3b. Note that two of the variance functions discussed in examples (i) and (ii) are approximately in line with the mixed model structure on the link scale, when $\phi$ is positive: the extra variation may be introduced by adding individual error terms on the link scale with variance $\phi$.

*Estimation of W*

We will now turn to the estimation of $W$. First we will have a look at a number of special, but practically relevant, cases.

1. Log link and quadratic variance function (for quantitative response variables):

$$g(\mu) = \log(\mu), \quad V(\mu) = \phi\mu^2. \tag{11}$$

Now $w = 1$ and $\sigma_0^2 = \phi$, i.e all weights are equal. This covers e.g. the analysis of sample variances under a factorial structure.

2. Logit link and "quadratic" variance function (e.g. binomial data):

$$g(\mu) = \log\left(\frac{\mu}{n-\mu}\right), \qquad V(\mu) = \phi\,\frac{\mu^2(n-\mu)^2}{n^2}.$$

Again $w = 1$ and $\sigma_0^2 = \phi$. An example is the "leaf-blotch on barley" data, described in McCULLAGH and NELDER (1989), §9.2.4. In this example percentages of leaf area affected are observed. The data is not binomial, but with $\mu$ a percentage, $g(\mu) = \log(\mu/(100-\mu))$ and $V(\mu) = \phi\mu^2((100-\mu)/100)^2$. The variance function may be obtained to first order by introducing a random effect with variance $\phi$ for logit $(\mu/100)$ and also follows as the limit for $n \to \infty$ of $\mathrm{Var}(100y/n) = 100^2 V(\mu, \phi)/n^2$, with $V(\mu, \phi)$ from (10).

3. When $g$ is the variance stabilizing transformation:

$$g'(\mu)^2 \propto \frac{1}{V(\mu)},$$

the weights are constant. (1) and (2) are special cases. Other, less important, examples are the square-root transformation in combination with Poisson data and the angular transformation in combination with binomial data.

4. Log link and power variance function:

$$g(\mu) = \log(\mu), \qquad V(\mu) = \phi\mu^{\alpha},$$

with $\alpha$ known. Then:

$$w^{-1} = E_u(\phi\mu^{\alpha-2}) = \phi E_u(e^{(X'\beta+Z'u)(\alpha-2)}) = \phi e^{X'\beta(\alpha-2)} E_u e^{Z'u} \propto e^{x'\beta(\alpha-2)}.$$

The weights do not depend on the distribution of $u$. Estimates for quantities $(x_1' - x_2')\beta$ may be obtained from an ordinary least squares fit on $\zeta$, ignoring the correlation structure. (1) is a special case.

5. Logit link and binomial variance function:

$$g(\mu) = \mathrm{Log}\left(\frac{\mu}{n-\mu}\right), \quad V(\mu) = \frac{\mu(n-\mu)}{n}, \quad \text{then}$$

$$g'(\mu) = \frac{1}{V(\mu)},$$

a property defining canonical link functions, and

$$w^{-1} = E_u\left(\frac{1}{V(\mu)}\right) = \frac{e^{-x'\beta}E_u(e^{-z'u}) + e^{x'\beta}E_u(e^{z'u}) + 2}{n}.$$

When the $u$'s are symmetrically distributed:

$$w^{-1} \propto \frac{E_u(e^{z'u})\cosh(x'\beta) + 1}{n},$$

and for normally distributed $u$'s:

$$w^{-1} \propto \frac{e^{\sum \sigma_i^2/2}\cosh(x'\beta) + 1}{n}.$$

For large $\sigma_i^2$ relative to $\beta$: $w^{-1} \propto \cosh(x'\beta)/n$. For small $\sigma_i^2$ relative to $\beta$: $w^{-1} \propto (\cosh(x'\beta) + 1)/n$.
Often for binary data the $\sigma_i^2$ are small, $x'\beta$ may be estimated by ordinary least squares on $\zeta$.

Generally, an obvious estimate for $w^{-1}$ is $\hat{w}^{-1} = V(\hat{\mu})g'(\hat{\mu})^2$, where $\hat{\mu}$ is obtained from the first step of the estimation procedure. Observe that $V(\hat{\mu})g'(\hat{\mu})^2$ may often be an accurate prediction for $V(\mu)g'(\mu)^2$, but that does not generally imply that it is a consistent estimator for $E_u(V(\mu)g'(\mu)^2)$. To that end the variance components $\sigma_i^2$ have to be relatively small, otherwise $\hat{w}^{-1}$ may be an asymptotically unbiased but inconsistent estimator for $w^{-1}$. When $\hat{w}^{-1} = V(\hat{\mu})g'(\hat{\mu})^2$, it follows from (4) that the lefthand sides of (9) will equal 0 in step 2, or

$$X'\hat{W}(g(\hat{\mu}) - g(\mu)) = 0 \quad \text{and} \quad Z'\hat{W}(g(\hat{\mu}) - g(\mu)) = \sigma_0^2\,\hat{G}^{-1}u,$$

the $g(\hat{\mu})$ are playing the role of observations on the scale of the link function.

In many cases it will be possible to improve on $\hat{w}$. For the logit link and binomial variance function in the context of a split plot, for instance, the following procedure may be useful: from estimates for $\mu$ (step 1) and $X\beta$ (ordinary least squares on $\zeta$ after step 1), residuals $\hat{u}$ may be recovered. An improved estimator, say $\bar{w}$, may be obtained by taking bootstrap samples $\hat{u}_{(1)} \ldots \hat{u}_{(B)}$ and evaluating $\bar{w}^{-1}$ as the mean of $V(\hat{\mu}_{(s)})g'(\hat{\mu}_{(s)})^2$, $s = 1 \ldots B$, with $\hat{\mu}_{(s)}$ the mean $\mu$ evaluated in $\hat{\beta}$ and $\hat{u}_{(s)}$. One advantage of using an improved estimator, more closely approximating $E_u(V(\mu)g'(\mu)^2)$, may be that weights are "smoothed", reducing instability due to the presence of a few extreme weights.

*(Asymptotic) properties of the estimators*

Properties of the estimators should follow from the relevant estimation equations, e.g. (4), (5) and (6) for steps 1, 2. For steps 1, 2, 3b estimation equations follow from (5) and (8) or equivalently (9), replacing $\hat{\mu}$ by $\mu$. Equations (9) simplify to:

$$X'W \operatorname{diag}(g'(\mu))(y-\mu) = 0,$$

$$Z'W \operatorname{diag}(g'(\mu))(y-\mu) = \sigma_0^2 G^{-1} u.$$

Clearly these equations are not easy to tackle. The asymptotics of QL (McCULLAGH, 1983) and (iterated) MINQUE (BROWN, 1976; RAO and KLEFFE, 1988), see also MILLER (1977), for concistently estimated weights ($\sigma_i^2 \to 0$), offer some justification for "large" samples and "small" components of variance. Genstat 5 (1987, 1990) produces approximate variances and covariances for estimated fixed effects and components of variance and mean squared errors for the predictions of the random effects for a LMM under normality. These approximations, obtained after step 2 or its last repeat, may be used for the final estimates and predictions in the GLMM. The assumption of normality can be relaxed, but at the least the kurtosis should be close to 0 for the random effects.

Simulation will have to show how well the estimation procedure performs for practical sample sizes. A Monte Carlo study for over-dispersed binomial data is in progress and results will be reported elsewhere.

With an additional non-multiplicative parameter $\phi$ in the conditional variance function, variability due to the estimation of $\phi$ is ignored. In some instances this may not be a serious problem, e.g. for $V(\mu, \phi) = \mu^{\phi}$, $\phi$ is usually restricted to the values $\phi = -1, 0, 1, 2, 3$. In other situations, e.g. $V(\mu, \phi) = \mu(1-\mu/n)(1+\phi(n-1))$ for "binomial data" where $\phi$ is a correlation coefficient, the ignored variability may seriously affect test results obtained from step 2. Even for independent data the latter problem is still unresolved.

The use of iterated MINQUE, which is equivalent to REML, may be expected to reduce the bias in the estimation of the variance components, relative to maximum likelihood, for normally distributed random effects.

## 5 Analysis of some data-sets

*The preparation of chocolate cakes*

This is hardly a realistic experiment, but it serves for a comparison with a quasi-likelihood based method for (balanced) data with a multiplicative structure for fixed and random effects from FIRTH and HARRIS (1991). The data of this experiment is from COCHRAN and COX (1957), p. 299. Three recipes for preparing the batter for a chocolate cake were compared. In addition, six different baking temperatures were tested. From a mix made by any recipe, six cakes were baked, one at each temperature. There were 15 replications, replicates representing time differences. The response variable is a "breaking angle", measured for each cake. The 45 batches of cake mix may be considered as "whole plots", with recipes and replicates as whole plot treatment factors. The 6 portions of each batch used to bake the cakes are the "sub plots", with temperature as a sub plot treatment factor. Firth and Harris estimate fixed effects from the quasi-likelihood equations (for non-diagonal covariance matrix of the observations), which for this particular type of model is shown to be equivalent to maximum likelihood based on the gamma distribution. Estimates for variance components are

obtained from rather arbitrarily chosen quadratic forms. For non-diagonal covariance matrices the quasi-likelihood $Q$ is defined by a, generally path dependent, line integral. A particular path is chosen and test results are obtained by comparing quasi-deviances $-2Q$, referring differences to chi-square distributions, using appropriate scaling factors. For analysis of balanced models with multiplicative effects and errors see also ENGEL, J. (1990) and the next data-set on soldering failures of printed circuit boards.

$$Y = e^{x'\beta}\varepsilon_1\varepsilon_2, \quad E(\varepsilon_i) = 1, \quad \mathrm{Var}(\varepsilon_i) = \phi_i, \quad i = 1,2, \quad \varepsilon_1, \varepsilon_2 \text{ independent.}$$

Conditional upon whole-plot errors $\varepsilon_1$:

$$\mu = E(Y \mid \varepsilon_1) = e^{x'\beta}\varepsilon_1,$$

$$\log(\mu) = x'\beta + \log(\varepsilon_1) = (x'\beta - \tfrac{1}{2}\phi_1) + u_1,$$

$$V(\mu) = \mathrm{Var}(y \mid \varepsilon_1) = \phi_2\mu^2,$$

where $\frac{1}{2}\phi_1$ is included in the general mean on the log scale, $u_1$ is the whole-plot error on that scale: $u_1 = \log(\varepsilon_1) + \frac{1}{2}\phi_1$ and

$$E(u_1) \approx 0, \quad \mathrm{Var}(u_1) = \mathrm{Var}(\log(\varepsilon_1)) \approx \mathrm{Var}(\varepsilon_1) = \phi_1.$$

In the notation of this paper: $\sigma_1^2 = \phi_1$, the variance component for batches, and $\phi = \phi_2$, the dispersion parameter of the extended variance function and residual component of variance on the log-scale. As was shown in §4, case (1), expression (11): $w = 1$. Estimates for the components of variance and $P$-values for the fixed effects $R$ and $T \times R$ ($R$ = recipes, $T$ = temperature), are shown in Table 1 for our procedure, for ANOVA on log transformed breaking angles and for the analysis of Firth and Harris. $P$-values for the main effects of temperature and replicates are $< 0.001$ in all analyses and omitted from the table.

Table 1. Some results for the chocolate cake data

| Type of analysis | $\sigma_1^2$ | $\phi_2$ | $P_{T\times R}$ | $P_R$ |
|---|---|---|---|---|
| GLMM | 0.0045 (0.0021) | 0.0191 (0.0019) | 0.50 | 0.15 |
| log(angle) and ANOVA | 0.0048 (0.0022) | 0.0192 (0.0019) | 0.52 | 0.16 |
| Firth and Harris | 0.004 | 0.0219 | 0.61 | 0.12 |

GLMM steps 1, 2 yield the same results as steps 1, 2, 3a and steps 1, 2, 3b. From the table it can also be observed that ANOVA on log transformed breaking angles (assuming in fact the log-normal distribution with whole-plot variance $\log(1 + \phi_1)$ and residual variance $\log(1 + \phi_2)$) yields virtually the same results as steps 1, 2 for the GLMM. This is not surprising for observations with relatively small variation in the means (so that $g(y)$ and its first order approximation $\zeta$ are close).

*Soldering failures in print panels*

The data is from an experiment with print panels where for each panel the number of soldering failures is observed. The experiment has been carried out with five replica-

tions at each combination of three soldering locations and two soldering methods. The thirty panels are the main plots of a split plot design. The sub-plot factor, applied to smaller sub-panels, is the type of copper pattern, at two levels. This data has been analysed by ENGEL, J. (1986, 1990). The data is typically Poisson-type, although extra-Poisson variation may exist. This is the approach taken in ENGEL (1987). In ENGEL (1990) a multiplicative model, both for fixed and random effects, similar to FIRTH and HARRIS (1991) is assumed. Separate analyses for the error-strata are performed, based on a QL approach with a gamma-type variance function and log link, critically depending on the balance of the design. Estimates for components of variance are obtained by equating Pearson chi-square statistics or quasi-deviances to their expectations. The analysis in ENGEL (1986) is also a combination of separate analyses on the whole- and sub-plot level, employing the Dirichlet multinomial and the negative binomial distribution. At the lowest level, observations are assumed to follow Poisson distributions. Some results for various models and methods for analysis are shown in Table 2, $\sigma_1^2$ is the whole-plot variance on the log scale, $\phi$ the (over)dispersion parameter for the sub-plots, $L \times M \times P$ the three factor interaction.

Table 2. Some results for the print panel data

| Model/analysis | | $\hat{\sigma}_1^2$ | $\hat{\phi}$ | $P_{L\times M\times P}$ |
|---|---|---|---|---|
| GLMM | Steps 1, 2 | 0.163 (0.072) | 0.98 (0.28) | 0.09 |
| $(V(\mu,\phi)=\phi\mu)$ | Steps 1, 2, 3a | 0.189 (0.074) | 0.86 (0.25) | 0.06 |
| | Steps 1, 2, 3b | 0.193 (0.077) | 0.90 (0.26) | 0.07 |
| GLMM $(V(\mu,\phi)=\phi\mu^2)$ | | 0.260 (0.098) | 0.142 (0.041) | 0.01 |
| ANOVA and Log transformation | | 0.248 (0.097) | 0.156 (0.045) | 0.02 |
| ENGEL (1986) | | - | Fixed at 1 | 0.10 |
| ENGEL (1990) Approach QA1 | | 0.205 (-) | 0.152 (-) | 0.01 |
| | | 0.199 (-) | 0.142 (-) | |

For the approach referred to as QA1 in ENGEL, J. (1990), the first line corresponds to an estimate $\hat{\phi}$ derived from a deviance and the second line to an estimate from an appropriate Pearson chi-square statistic. Since the estimator $\hat{\sigma}_1^2$ depends on $\hat{\phi}$, there are also two estimates for the whole-plot component of variance. For the GLMM with unequal weights $(V(\mu,\phi)=\phi\mu)$, $P$-values for the three factor interaction are derived by referring the Wald statistic (BUIST and ENGEL, 1991, 1992) to a chi-square distribution. For ANOVA on log transformed data and for the GLMM with variance function $\phi\mu^2$, where weights are equal and the balance of the design carries over to the log scale, $F$-tests are used. Results for the GLMM with $V(\mu,\phi)=\phi\mu^2$ do not change from step 1, 2 to step 3a or 3b and also are close to the results of the ANOVA on log transformed data and of QA1. It is easily shown that for balanced data and the variance stabilizing link function the estimate for $\phi$ from step 2 is equal to the traditional estimator obtained from Pearson's chi-square in step 1. Inference with respect to the three-factor-interaction to some extent does depend on the variance function assumed. It is hard to decide which variance function is most appropriate on the basis of the data, although the nature of the

problem seems to support the assumption of Poisson variation at the sub-plot level. The estimated dispersion factor is in perfect agreement with this assumption.

*Radiation of cancer cells*

The data set originates from an experiment to measure the mortality of cancer cells under radiation and is presented in SCHALL (1991). Four hundred cells were placed on a dish, and at each of nine occasions three dishes were irradiated. After irradiation the number of surviving cells was counted in each dish. To establish the natural mortality data corresponding to a zero-dose was analyzed. Our results will be compared with Schall's REML type algorithm, see also §6. Considering, apart from the binomial variation at cell level, with a multiplicative dispersion parameter $\phi$, only one component of variance $\hat{\sigma}_1^2$ between occasions, at the logistic scale, steps 1 and 2 result in estimates $\hat{\sigma}_1^2 = 0.221$ (0.144) and $\hat{\phi} = 1.819$ (0.606). Estimates obtained by Schall are almost identical: $\hat{\sigma}_1^2 = 0.225$ and $\hat{\phi} = 1.810$. Steps 1, 2 and 3b result in estimates $\hat{\sigma}_1^2 = 0.221$ and $\hat{\phi} = 1.817$, with standard errors as before. $\phi > 1$ indicates the presence of extra-binomial variation. One way to "explain" the over-dispersion is to introduce an additional component of variance $\sigma_1^2$ between dishes on the logistic scale. Schall still estimates a multiplicative dispersion parameter $\phi$ and for comparison we do the same, although now it seems natural to fix $\phi$ at value 1, i.e. drop $\phi$ from the model. With steps 1, 2 and 3b, analysing the binary observations per cell, i.e. $n = 1$, estimates $\hat{\sigma}_1^2 = 0.221$, $\hat{\sigma}_2^2 = 0.0098$ and $\hat{\phi} = 1.002$ are found. Schall obtains $\hat{\sigma}_1^2 = 0.222$, $\hat{\sigma}_2^2 = 0.010$ and $\hat{\phi} = 0.937$.

## 6 Discussion

In an ordinary LMM the random effects can be integrated out of the simultaneous likelihood of observations $y$ and random effects $u$ analytically. Numerical problems mainly involve storage and inversion of large matrices, which to a large extent can be overcome by exploiting the structure of the covariance matrix of the observations, see ENGEL, B. (1990).

In a GLMM with full distributional assumptions, e.g. normality for the random effects $u$, integration can generally not be performed analytically and maximum likelihood estimation is often bogged down by cumbersome numerical integration routines. Integration is usually by Gauss-Hermite quadrature (ABRAMOWITZ and STEGUN, 1965, p. 924), offering serious problems when a large number of quadrature points is needed and when there are crossed random effects in the model. Little seems to be known about robustness with respect to distributional assumptions for the random effects.

A distinct advantage of the estimation procedure in this paper is that many of the results for LMM's carry over to GLMM's, such as procedures for constructing confidence intervals for components of variance or approximate $t$-tests for contrasts of fixed effects accounting for variation due to estimation of the components of variance, see ENGEL, B. (1990). The combination of QL and MINQUE, both least squares procedures, offers some scope for robustness. Clearly for a number of practical problems, e.g. relatively small components of variance and fairly large binomial denominators or

Poisson means, steps 1 and 2 should produce acceptable results. Extension of the estimation procedure with step 3a or 3b is intuitively attractive and may remove possible inefficiency following from step 1. A formal justification of steps 1, 2 and 3b will have to be based on the corresponding estimating equations, which is a tough nut to crack.

Recently, related estimation procedures have been proposed by BRESLOW and CLAYTON (1991) and SCHALL (1991). Schall's REML based algorithm is similar to an extension of our estimation procedure (steps 1, 2 and 3b), except that MINQUE represents a step from Fisher scoring and not from the EM algorithm for REML. The random character of the conditional variances $V(\mu)g'(\mu)^2$, through their dependence on the random effects $u$, seems to be completely ignored: the elements of a supposed covariance matrix in expression (2.3) in Schall's paper are actually random variables. Breslow and Clayton's PQL approach is motivated by quasi-likelihood arguments. The random effects are assumed to be normally distributed, which is equivalent to the use of a sum of extended quasi-likelihoods for identity link and constant variance functions for the sub-vectors $u_1 \ldots u_c$ of $u$. The quasi-conditional likelihood of $y$ given $u$ is replaced by a quadratic approximation in terms of the random effects. The quadratic approximation is around the (current) predictions $\hat{u}$. The random effects are easily integrated out of the product of the exponentials of the approximate quasi-conditional-likelihood of $y$ given $u$ and the quasi-likelihood of $u$. This yields an approximate marginal quasi-likelihood for the observations $y$. In the derivation, where mathematically convenient, some terms, e.g. $g'(\mu)^2V(\mu)$, are assumed to vary slowly with $\mu$ and ignored. Conditional quasi-deviance residuals are replaced by Pearson residuals, which gives a pseudo-likelihood flavour to the method. Not surprisingly the combination of a quadratic approximation and Pearson residuals leads to a normal log likelihood for the IRLS working variable $\zeta$. A REML type adjustment for loss of degrees of freedom due to estimation of fixed effects, rather poorly motivated in this context, finally yields a REML log likelihood. So, although from quite a different starting point, PQL results in the same algorithm as steps 1, 2, 3b, possibly except for (minor) differences in the order in which parameter estimates and predictions for the random effects are updated.

Both the quadratic approximation of the quasi-conditional-likelihood and the approximation of quasi-deviance residuals by Pearson residuals in Breslow and Clayton's paper will improve under "small dispersion asymptotics", e.g. large totals $n$ for binomial data or large means for Poisson data. Similar conditions will improve the performance of the MINQUE procedure in steps 2, 3a and 3b and the usefulness of the working variable from step 1. The assumption, in the derivation of PQL, that $g'(\mu)^2V(\mu)$ varies only slowly with $\mu$, also requires that components of variance are relatively small.

LONGFORD (1991) develops an approximate maximum likelihood method under full distributional assumptions, e.g. logistic regression with additional normal random effects on the logit scale. He also utilizes a quadratic approximation, but around 0 and not around $\hat{u}$, again implying that components of variance should not be too large.

For the data sets we analysed, including the examples in §5, differences with results from specialised methods, e.g. for special link and variance functions or for balanced designs only, were generally small. Present research includes a simulation study of the

properties of estimates from steps 1, 2 and 1, 2, 3a or 3b, and the quality of approximate variances and covariances and Wald tests derived from the last REML step. A comparison with maximum likelihood for normally distributed random effects and a GLM at the lowest stratum, both with respect to efficiency and robustness, is also considered.

Should the estimation procedure presented in this paper gain in respectability, then a general and useful tool will have become available to tackle problems which so far are a source of considerable discomfort to many an applied statistician.

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# Chapter 5

## Analysis of a generalized linear mixed model: a case study and simulation results

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Application of IRREML to a practical problem involving carcass classification data. The data are fractions. This is a first attempt to increase confidence in the estimation procedure by looking at simulation results based on the classification problem.

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# Analysis of a Generalized Linear Mixed Model: a Case Study and Simulation Results

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*Summary*

A class of generalized linear mixed models can be obtained by introducing random effects in the linear predictor of a generalized linear model, e.g. a split plot model for binary data or count data. Maximum likelihood estimation, for normally distributed random effects, involves high-dimensional numerical integration, with severe limitations on the number and structure of the additional random effects. An alternative estimation procedure based on an extension of the iterative re-weighted least squares procedure for generalized linear models will be illustrated on a practical data set involving carcass classification of cattle. The data is analysed as overdispersed binomial proportions with fixed and random effects and associated components of variance on the logit scale. Estimates are obtained with standard software for normal data mixed models. Numerical restrictions pertain to the size of matrices to be inverted. This can be dealt with by absorption techniques familiar from e.g. mixed models in animal breeding. The final model fitted to the classification data includes four components of variance and a multiplicative overdispersion factor. Basically the estimation procedure is a combination of iterated least squares procedures and no full distributional assumptions are needed. A simulation study based on the classification data is presented. This includes a study of procedures for constructing confidence intervals and significance tests for fixed effects and components of variance. The simulation results increase confidence in the usefulness of the estimation procedure.

*Key words:* Components of variance; Mixed model; GLMM; REML; Overdispersion.

## 1. Introduction

Key properties of the linear model $y = \mu + e$ for observations $y$ with means $\mu$ and variances $\sigma^2$ are (i) linear dependence of the mean $\mu$ on parameters $\beta_1, \ldots, \beta_p$: $\mu = x'\beta$, with $x = (x_1 \ldots x_p)'$ known and $\beta = (\beta_1 \ldots \beta_p)'$ unknown, (ii) (functional) independence of the variance $\sigma^2$ of the mean $\mu$ and (iii) mutual independence of observations $y$. Important extensions of the linear model are the linear mixed model (LMM) (Searle, Casella and McCulloch, 1992) and the generalized linear model (GLM) (McCullagh and Nelder, 1989).

In a LMM observations may be interdependent, i.e. point (iii) is relaxed. Additional to the residual error terms $e$, random effects $u_1 \ldots u_q$ are introduced in

the model: $y = x'\beta + z'u + e$, with $z = (z_1 \ldots z_q)'$ known and $u = (u_1 \ldots u_q)'$ unknown. Observations with elements of $u$ in common are (positively) correlated. An example is the split plot model where the elements of $u$ are the "whole plot errors" and the correlation between observations on the same whole plot is $\sigma_u^2/(\sigma_u^2 + \sigma_e^2)$, where $\sigma_u^2$ and $\sigma_e^2$ are components of variance "between" and "within" whole plots respectively. In a GLM observations are independent. The mean $\mu$ still depends on a linear combination $x'\beta$, now referred to as the linear predictor $\eta$, but through a known link function $g$: $g(\mu) = \eta = x'\beta$. The variance may be proportional to a known function of the mean: $\text{var}(y) = \phi V(\mu)$. So, (i) and (ii) are relaxed. Well known examples are the logistic regression model for binomial proportions and the log-linear model for Poisson counts.

Sometimes both GLM and LMM features are needed, e.g. a split plot model for proportions. A class of generalized linear mixed models (GLMM) may be obtained by adding random effects to the linear predictor in a GLM structure: $\eta = x'\beta + z'u$, see e.g. ANDERSON and HINDE (1988), PREISLER (1988), IM and GIANOLA (1988) and JANSEN (1990, 1992). The estimation procedure suggested by these authors is maximum likelihood, e.g. for binomial data with normally distributed random effects on the logit scale. To obtain the likelihood, random effects have to be "integrated out". This involves high-dimensional numerical integration, e.g. Gauss-Hermite quadrature (ABRAMOWITZ and STEGUN, 1965, p. 924), with severe limitations on the number and structure of random effects in the linear predictor. Numerical problems with two crossed random effects are insurmountable. In ENGEL and KEEN (1994) an estimation procedure is presented that does not suffer from these limitations. This procedure is a straightforward extension of the iterative re-weighted least squares (IRLS) algorithm for GLMs (for IRLS see e.g. MCCULLAGH and NELDER, 1989, §2.5), replacing repeated use of weighted least squares on the adjusted dependent variate by repeated use of LMM methodology. This approach is illustrated on carcass classification data. Calculations are performed with standard software for GLMs and LMMs in Genstat 5 (1993). Some aspects of the data are discussed in section 2. The analysis is presented in section 3. Simulation results based on the classification data are presented in section 4. Section 5 includes a brief discussion of the relation to other alternatives for maximum likelihood estimation, i.e. GIANOLA and FOULLEY (1983), HARVILLE and MEE (1984), GILMOUR, ANDERSON and RAE (1985), SCHALL (1991), BRESLOW and CLAYTON (1993) and MCGILCHRIST (1994).

## 2. The Classification Data

In slaughterhouses in the European Community cattle carcasses are visually assessed according to the EC classification system (WALSTRA, 1991). This includes visual assessment of conformation, supported by photographic standards. There are five main classes for conformation: E, U, R, O and P and each main

class may be subdivided into three sub classes. Conformation E corresponds to the convex to superconvex profiles, very rounded with exceptional muscle development. Conformation P corresponds to the concave to very concave profiles, with poor muscle development. The data set comprises 575 batches of carcasses from 23 Dutch slaughterhouses. Batch sizes vary from 25 to 51 with an average of 46.6. Each batch is independently classified by one of 4 experts and one of 52 classifiers. The data set is very unbalanced as illustrated by Table 1.

Table 1

Number of batches per classifier and slaughterhouse, illustrating the unbalancedness of the data

| | Slaughterhouse | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | Total |
| Class. | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 | – | – | – | – | 1 | – | 6 | 1 | – | – | – | 1 | – | – | – | – | 2 | – | – | – | 1 | – | – | 12 |
| 2 | – | 4 | – | – | – | 2 | – | – | – | – | – | – | – | – | – | 1 | – | – | 2 | – | – | – | 1 | 10 |
| 3 | – | – | – | – | – | – | – | – | – | – | – | – | 14 | – | – | – | – | – | – | – | 1 | – | – | 15 |
| 4 | – | – | – | – | – | – | – | – | – | – | – | 1 | 11 | – | – | – | – | – | – | – | – | 1 | – | 13 |
| 5 | – | – | – | – | 1 | – | 1 | 5 | – | – | 1 | – | – | – | – | – | 4 | – | – | – | – | – | – | 12 |
| 6 | 2 | 3 | – | – | – | 1 | – | – | – | 2 | – | – | – | 4 | – | – | – | 1 | – | – | – | – | – | 13 |
| 7 | – | – | – | – | 4 | – | 4 | – | – | – | – | – | – | – | 3 | – | 1 | – | 1 | – | – | – | – | 13 |
| 8 | – | – | – | – | – | – | 4 | – | – | – | – | – | – | – | 1 | – | 7 | – | – | – | – | – | – | 12 |
| 9 | – | – | – | – | – | – | 7 | – | – | – | 1 | – | – | – | – | – | 2 | – | – | – | – | – | – | 10 |
| 10 | – | 1 | – | – | – | – | – | – | – | – | – | – | – | – | 3 | 6 | – | – | 3 | – | – | – | 1 | 14 |
| 11 | – | – | – | – | – | – | – | – | 6 | 3 | – | – | – | 2 | – | – | – | 3 | – | – | – | – | – | 14 |
| 12 | – | – | – | – | – | – | 2 | 1 | – | – | 1 | – | – | – | 2 | – | 2 | – | – | – | – | – | – | 8 |
| 13 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 6 | 4 | – | – | 4 | – | – | – | – | 14 |
| 14 | – | – | – | – | – | – | 1 | 1 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 2 |
| 15 | – | – | – | – | – | – | – | – | 1 | – | – | – | – | 2 | – | – | – | 11 | – | – | – | – | – | 14 |
| 16 | – | – | – | – | – | 1 | – | – | – | – | – | – | – | 1 | 5 | – | 2 | – | 4 | – | – | – | 2 | 15 |
| 17 | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | – | 2 |
| 18 | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 1 | – | – | – | – | 1 |
| 19 | – | – | 3 | 2 | – | – | – | – | – | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | 6 |
| 20 | – | 4 | – | – | – | – | – | – | – | – | – | – | – | 4 | – | – | – | – | – | – | – | – | – | 8 |
| 21 | – | – | – | – | – | – | – | – | 1 | 2 | – | – | – | 5 | – | – | – | 3 | 2 | – | – | – | – | 13 |
| 22 | – | – | – | – | – | – | – | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | – | – | 1 |
| 23 | – | – | 9 | 3 | – | – | – | – | – | – | – | – | – | – | – | 3 | – | – | – | – | – | – | – | 15 |
| 24 | – | – | 2 | – | – | – | – | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | – | – | 3 |
| 25 | – | – | – | – | 1 | – | 2 | 4 | – | – | – | 1 | – | – | – | – | 7 | – | – | – | – | – | – | 15 |
| 26 | – | – | 6 | 3 | – | – | – | – | – | – | – | – | – | 1 | – | 1 | – | – | – | – | – | – | – | 11 |
| 27 | – | – | – | – | – | – | – | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | – | – | 1 |
| 28 | – | 1 | – | – | – | – | – | – | – | – | – | – | – | – | – | 8 | – | – | 6 | – | – | – | 1 | 16 |
| 29 | – | 2 | – | – | – | 2 | – | – | – | – | – | – | – | – | – | 2 | – | – | 4 | – | – | – | 3 | 13 |
| 30 | 1 | – | – | – | – | – | – | – | – | 4 | – | – | – | 3 | – | – | – | – | – | 4 | – | – | – | 12 |
| 31 | – | – | – | – | – | – | – | – | – | – | – | 2 | 9 | – | – | – | – | – | – | – | – | 1 | – | 12 |
| 32 | – | – | – | – | – | – | – | – | – | – | – | 2 | 12 | – | – | – | – | – | – | – | 1 | – | – | 15 |
| 33 | – | – | – | – | – | – | 5 | – | – | – | – | 1 | – | – | – | – | 5 | – | – | – | 1 | – | – | 12 |
| 34 | – | – | – | – | 3 | – | 4 | – | – | – | – | 1 | – | 1 | – | – | – | – | – | – | – | – | – | 9 |

Table 1 (continued)

| | Slaughterhouse | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | Total |
| Class. | | | | | | | | | | | | | | | | | | | | | | | | |
| 35 | – | – | – | – | – | – | 1 | 9 | – | – | 1 | – | – | – | – | – | 2 | – | – | – | – | – | – | 13 |
| 36 | – | – | – | – | – | – | 3 | 2 | – | – | 1 | – | – | – | – | – | – | – | – | – | – | – | – | 6 |
| 37 | – | – | – | – | 2 | – | 3 | 2 | – | – | 2 | – | – | – | – | – | 3 | – | – | – | – | – | – | 12 |
| 38 | – | – | – | – | – | – | – | – | 1 | 4 | – | – | – | 4 | – | – | – | 4 | – | 1 | – | – | – | 14 |
| 39 | – | – | – | – | – | – | – | – | – | – | – | 1 | 10 | 1 | – | – | – | – | – | – | – | 2 | – | 14 |
| 40 | – | – | – | – | – | – | – | – | – | 2 | – | – | – | 1 | – | – | – | – | – | – | – | – | – | 3 |
| 41 | – | – | – | – | – | – | 1 | – | – | – | – | 1 | – | – | – | – | 4 | – | – | – | – | – | – | 6 |
| 42 | 2 | – | – | – | – | – | – | – | 1 | 3 | – | – | – | 6 | – | – | – | – | – | – | – | – | – | 12 |
| 43 | – | – | – | – | 1 | – | 7 | 3 | – | – | – | – | – | – | – | – | 3 | – | – | – | – | – | – | 14 |
| 44 | 1 | – | – | – | – | – | – | – | – | – | – | – | – | 3 | – | – | – | – | – | – | – | – | – | 4 |
| 45 | – | – | – | – | – | – | – | – | 1 | – | – | – | – | 3 | – | – | – | 4 | – | – | – | – | – | 8 |
| 46 | – | – | – | – | – | – | – | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | – | – | 1 |
| 47 | – | 5 | – | – | – | 1 | – | – | – | – | – | – | – | – | – | – | – | – | 2 | – | – | – | 4 | 12 |
| 48 | – | – | – | – | – | – | 1 | – | – | – | – | 1 | – | – | – | – | 3 | – | – | – | – | – | – | 5 |
| 49 | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | – | – | 2 | – | – | – | – | – | – | 3 |
| 50 | 2 | 1 | – | – | – | – | 10 | 2 | 1 | 1 | 1 | – | 2 | 5 | 3 | – | 7 | 1 | 7 | – | – | – | – | 43 |
| 51 | – | – | – | – | – | – | – | – | – | – | 1 | – | – | – | – | – | – | – | – | – | – | – | – | 1 |
| 52 | – | – | – | – | – | – | 5 | – | – | 1 | – | – | 7 | 9 | – | 1 | 10 | 7 | 8 | – | – | – | – | 48 |
| Total | 8 | 21 | 20 | 8 | 13 | 7 | 69 | 30 | 12 | 22 | 9 | 12 | 65 | 59 | 24 | 27 | 66 | 34 | 44 | 5 | 4 | 4 | 12 | 575 |

Proportions of equal scores per batch are analysed, introducing classifiers as random effects. Interest lies in variation between classifiers, i.e. in components of variance associated with main effects and interactions for classifiers. The "raw" mean of the fractions of agreement over all the batches is 0.63. The means for the experts are 0.60, 0.61, 0.63 and 0.65. Means for the slaugterhouses vary from 0.52 to 0.77.

## 3. Analysis of the Classification Data

### 3.1 *Getting started*

Estimation starts with a logistic regression model (COX and SNELL, 1990), including classifier effects as fixed effects. Observation $y_t$ for batch $t$, $t = 1 \ldots N$, is the fraction of carcasses with an equal score from expert and classifier. Expectation $\mu_t$ of $y_t$ is the probability of agreement between expert and classifier for a typical carcass at the particular slaughterhouse. The linear predictor $\eta_t = \log(\mu_t/(1-\mu_t))$ is a combination of main effects and interactions for slaughterhouses, experts and classifiers. Visual assessment of conformation is influenced by many factors, most of which are not very well known. Over-dispersion is quite likely and the variance of an observation is assumed to be:

$$\text{var}(y_t) = \phi \mu_t (1 - \mu_t)/n_t, \tag{1}$$

where $\phi$ is an unknown dispersion factor and $n_t$ is the batch size.

Parameters are estimated by maximum quasi-likelihood (QL) (McCullagh and Nelder, 1989, Ch. 9) with the IRLS algorithm, using standard software in Genstat 5. Quasi-deviances for various models fitted to the data are presented in Table 2. Tests for interactions are derived by scaling the difference between the deviances of two nested models by an estimate $\hat{\phi}$ for the dispersion factor, referring the result to a chi-square distribution. Estimate $\hat{\phi}$ is equal to Pearson's chi-square statistic divided by its degrees of freedom (McCullagh and Nelder, 1989, §4.5. and Ch. 9), evaluated for the largest of the two models. Model 5, with main effects and interactions between experts and slaughterhouses and between experts and classifiers, describes the data adequately and will be used in subsequent steps of the estimation procedure. In this model $\hat{\phi} = 1.29$ (0.094), where the standard error (in parentheses) is based on approximation by a chi-square distribution with 375 degrees of freedom. The same approximation shows that $\phi$ is significantly larger than 1.

Table 2

Quasi-deviance and Pearson's chi-square statistic for various models fitted to the classification data. C, S and E denote main effects for classifiers, slaughterhouses and experts respectively, C.S denotes interaction between classifiers and slaughterhouses etc.

| Model | Quasi-deviance | Degrees of freedom | Pearson's chi-square |
|---|---|---|---|
| 1 C+S+E+C.S+C.E+S.E+C.S.E | 375.0 | 284 | 369.1 |
| 2 C+S+E+C.S+C.E+S.E | 377.8 | 288 | 372.0 |
| 3 C+S+E+C.S+C.E | 429.9 | 309 | 423.5 |
| 4 C+S+E+C.S +S.E | 470.5 | 339 | 461.9 |
| 5 C+S+E +C.E+S.E | 490.4 | 375 | 482.9 |
| 6 C+S+E | 725.9 | 498 | 712.5 |
| 7 C+S+E +C.E | 562.3 | 409 | 553.6 |
| 8 C+S+E +S.E | 643.1 | 454 | 631.1 |

For use in subsequent steps of the estimation procedure note that the adjusted dependent variate $\zeta_t$ of the IRLS algorithm, corresponding to the fitted values $\hat{\mu}_t$, is:

$$\zeta_t = (y_t - \hat{\mu}_t)\, g'(\hat{\mu}_t) + g(\hat{\mu}_t).$$

Approximate mean and variance are:

$$E(\zeta_t) \approx g(\mu_t) \quad \text{and} \quad \text{var}(\zeta_t) \approx g'(\hat{\mu}_t)^2 \,\text{var}(y_t), \tag{2}$$

as follows from $(\mu_t - \hat{\mu}_t)\, g'(\hat{\mu}_t) \approx g(\mu_t) - g(\hat{\mu}_t)$, where $g'$ is the derivative of the link function with respect to $\mu_t$.

### 3.2 *Fitting a LMM to the adjusted dependent variate*

Classifier effects will now be introduced as random effects on the logit scale. Let $X$ and $Z=(Z_1, Z_2)$ be the design matrices for the vectors $\beta$ and $u=(u_1', u_2')'$ of fixed and random effects, respectively. Elements of $u$ are uncorrelated with zero means and variances $\sigma_1^2$ for the classifier main effects in vector $u_1$ and $\sigma_2^2$ for classifier * expert interactions in vector $u_2$. Without loss of generality $X$ is assumed to be of full rank. The total variance on the logit scale is $\sigma^2=\sigma_1^2+\sigma_2^2$ and the correlation between any two random contributions for the same classifier but different experts is $\varrho=\sigma_1^2/(\sigma_1^2+\sigma_2^2)$. For a formal derivation of the model see section 5. The vector of linear predictors $\eta=\text{logit}(\mu)=X\beta+Zu$, where $\mu=E(y|u)$ is the vector of conditional means and $y$ the vector of observations. Conditional variances are $\text{var}(y_t|u)=\phi\,\mu_t(1-\mu_t)/n_t=\phi\,V(\mu_t)$, say.

The mean and variance presented in (2) are conditional upon the random effects. The marginal mean and covariance matrix are approximately:

$$E(\zeta)\approx X\beta \quad \text{and} \quad \text{var}(\zeta)\approx Z_1 Z_1'\sigma_1^2+Z_2 Z_2'\sigma_2^2+\phi\,\hat{W}^{-1},$$

where $\hat{W}$ is a diagonal matrix with diagonal elements $\hat{w}_t=(g'(\hat{\mu}_t)^2\,V(\hat{\mu}_t))^{-1}$. This is a LMM structure for $\zeta$ with weights $w_t$ on the "residual" error stratum and dispersion factor $\phi$ in the role of a residual error variance. For details see ENGEL and KEEN (1994).

Components of variance and dispersion factor $\phi$ are estimated by Iterated MInimum Norm Quadratic Unbiased Estimation (I-MINQUE).

Dependence of MINQUE (RAO, 1973, §4j) on a priori values disappears when it is iterated, using successive estimates as a priori values, yielding I-MINQUE with more attractive (asymptotic) properties (BROWN, 1976). I-MINQUE is essentially an iterated weighted least squares method, see SEARLE et al. (1992, Ch. 12), and there is no need for full distributional assumptions. Ignoring non-negativity constraints, estimating equations for restricted maximum likelihood (REML) (PATTERSON and THOMPSON, 1971) and I-MINQUE are the same (see e.g. SEARLE et al., 1992, p. 397–399), i.e. the two methods are operationally equivalent. We used the REML facilities of Genstat 5.

Estimating equations for the components of variance are:

$$\zeta' P Z_m A_m Z_m' P\zeta=\text{trace}(Z_m' P Z_m A_m), \quad m=0, 1, 2, \tag{3}$$

where $P=\Omega^{-1}-\Omega^{-1}X(X'\Omega^{-1}X)^{-1}X'\Omega^{-1}$, $\Omega=Z_1 Z_1'\sigma_1^2+Z_2 Z_2'\sigma_2^2+\phi\,\hat{W}^{-1}$, $A_0=\hat{W}^{-1}$ and $Z_0, A_1, A_2$ are identity matrices. Solutions are: $\hat{\sigma}_1^2=0.0144$ (0.0081), $\hat{\sigma}_2^2=0.0062$ (0.0083) and $\hat{\phi}=1.379$ (0.096) for the components for classifier main effects, classifier * expert interaction and residual (dispersion factor), respectively. Standard errors (in parentheses) are obtained with Genstat and based on Fisher information under normality for an ordinary LMM, see section 5.

Estimates $\hat{\beta}$ for the fixed effects and predictions $\hat{u}$ for the random effects may be obtained from the following mixed model equations (MMEs) (see e.g. SEARLE et al., 1992, §7.6.):

$$\begin{pmatrix} X'\hat{W}X & X'\hat{W}Z \\ Z'\hat{W}X & Z'\hat{W}Z+\phi G^{-1} \end{pmatrix} \begin{pmatrix} \beta \\ u \end{pmatrix} = \begin{pmatrix} X'\hat{W}\zeta \\ Z'\hat{W}\zeta \end{pmatrix}. \tag{4}$$

Here $\Omega$ and $G = \mathrm{Var}(u)$ are evaluated for the estimates $\hat{\sigma}_1^2$, $\hat{\sigma}_2^2$ and $\hat{\phi}$.

In a LMM $\hat{\beta}$ is the generalized least squares estimator, $\hat{u}$ is referred to as the best linear unbiased predictor (BLUP) (see e.g. ROBINSON, 1991). The MMEs can be reduced in size by elimination of main effects and interactions corresponding to a factor with many levels, typically the classifier main effects and expert * classifier interactions in the classification data. In animal breeding theory this process is referred to as absorption (see e.g. ENGEL, 1990). Genstat allows to define an absorbing factor, interactions with the absorbing factor are automatically absorbed as well. Equations (3) may be formed from bits and pieces of the MMEs (4) and their solution $(\hat{\beta}', \hat{u}')'$.

Here the estimation procedure might stop. However, it is quite tempting to update the adjusted dependent variate and weights, employing the estimates $\hat{\beta}$ and predictions $\hat{u}$ from (4), and repeat the LMM step until convergence. We will do so in the next section.

### 3.3 *Iterating on*

One step of MINQUE suffices in each repeat of the LMM step. MINQUE is equivalent to one step of the Fisher scoring algorithm for REML (SEARLE et al., 1992, p. 397–399). Genstat uses Fisher scoring and we simply restricted the algorithm to perform one step only. Final estimates are $\hat{\sigma}_1^2 = 0.0137$ (0.0082), $\hat{\sigma}_2^2 = 0.0092$ (0.0088) and $\hat{\phi} = 1.364$ (0.095), for classifier main effects, classifier * expert interaction and residual respectively. These estimates are very similar to those obtained in the previous section, as judged by their standard errors. The total variance $\hat{\sigma}^2 = \hat{\sigma}_1^2 + \hat{\sigma}_2^2 = 0.0229$ (0.0084) and the correlation $\hat{\varrho} = \hat{\sigma}_1^2/(\hat{\sigma}_1^2 + \hat{\sigma}_2^2) = 0.60$ (0.33).

With the Wald test (BUIST and ENGEL, 1992), after approximation with a chi-square distribution with 44 degrees of freedom, the interaction between experts and slaughterhouses is close to significance ($P = 0.06$). Estimated means on the logit scale for the 70 combinations of experts and slaughterhouses vary from $-0.2291$ (0.3564) to 1.2204 (0.4069). One way to proceed is to choose a number of typical values for the linear predictor and describe the variation between classifiers around those levels.

Suppose that $\eta$ is one of the typical values for a combination of expert and slaughterhouse. For a random classifier an approximate 0.95 prediction interval for the linear predictor is: $\eta \pm 1.96\ \hat{\sigma}$, say $(\eta_-; \eta_+)$. The corresponding 0.95 prediction interval for the probability of agreement is: $(1/(1+\exp(-\eta_-)); 1/(1+\exp(-\eta_+))$. For small $\sigma^2$ the average probability of agreement is approximately: $1/(1+\exp(-\eta))$, say $p(\eta)$, and the range of the interval is: $3.92\ \sigma\, p(\eta)\,(1-p(\eta))$.

Another approach, followed here, is to assume that slaughterhouse and expert * slaughterhouse effects are random as well, with the following results: $\hat{\sigma}_1^2 = 0.0143$ (0.0074), $\hat{\sigma}_2^2 = 0.0071$ (0.0076), $\hat{\sigma}_3^2 = 0.0092$ (0.0078), $\hat{\sigma}_4^2 = 0.0109$ (0.0077) and $\hat{\phi} = 1.379$ (0.094) for the classifier main effects, expert * classifier interaction,

slaughterhouses main effects, expert * slaughterhouse interaction and residual, respectively. The Wald test for experts is not significant ($P = 0.14$), indicating that differences between experts are relatively small. The mean levels for the 4 experts on the logit scale are: 0.3942 (0.0625), 0.4432 (0.0692), 0.5295 (0.0488) and 0.5473 (0.0609). The average standard error of a difference between two experts is 0.0769. The overall level is 0.4786 (0.0382). The total variance due to classifiers is $\hat{\sigma}^2 = 0.0214$ (0.0078) and correlation $\hat{\varrho} = 0.67$ (0.31). For $\eta = 0.4786$, the approximate 0.95 prediction interval for the probability of agreement is: (0.548; 0.683). Intervals of similar width are obtained for the separate experts. Hence, the range of the probability of agreement between classifier and expert is about 0.135 (0.024), due to differences between classifiers, around an average level of about 0.62 (0.02). The size of the range indicates that there is still scope for improvement.

Scaled residuals for $\zeta$ are equivalent to Pearson residuals for the original fractions of agreement evaluated for $\hat{\beta}$ and $\hat{u}$ from (4). Plots of these residuals do not indicate that the assumed variance (1) is inadequate. A normal probability plot of the residuals does not indicate any serious departures from normality for the random effects, which gives some reassurance for the use of the approximate variances and covariances (see section 5).

## 4. A Monte Carlo Study

Simulation is based on the classification data. To reduce the amount of calculation involved, the model is restricted to main effects only. Furthermore, conditional upon the classifiers, data are generated from binomial distributions. Consequently the dispersion factor $\phi$ is identical to 1, although it is assumed to be unknown in the estimation process. Random classifier effects are generated from a $N(0, \sigma_1^2)$ disribution. Several parameter configurations are studied. For each configuration 1000 simuations are performed. $\sigma_1^2$ and $\phi$ are updated until the absolute change in successive iterates is less than 0.0001 times the value of the last update but one. When this does not occur within 25 iterations, estimates from the 25th iteration are considered to be the final estimates. A negative value for $\sigma_1^2$ is replaced by 0.0001 of the estimate for $\phi$.

Note that in some problems it could make sense to allow the estimates to remain negative, as long as the covariance matrix on the link scale remains positive definite, thereby allowing for negative correlation on the link scale as well (e.g. SEARLE et al., 1992, § 11.2).

To see how some of the methods available for ordinary mixed models perform for a GLMM when applied to the adjusted dependent variate, the Wald test for fixed effects, two procedures for constructing a confidence interval for the ratio $\gamma = \sigma_1^2/\phi$ (SEELY and EL-BASSIOUNI, 1983; HARVILLE and FENECH, 1985) and for the "residual variance" $\phi$, and an F-test for the hypothesis $\sigma_1^2 = 0$, are studied.

In "ordinary" over-dispersion models, see e.g. BRESLOW (1990), WILLIAMS (1991), the Wald test, quasi-score test and quasi-likelihood ratio test are proposed for testing parameters in the linear predictor. Without full distributional assumptions the latter two tests have no obvious direct extension to the GLMM model. In BRESLOW and CLAYTON (1993) an approximate quasi-likelihood for a GLMM is derived, which motivates the estimating equations for the components of variance. However, it is not clear whether this leads to a suitable test criterion. The Wald test easily extends to GLMMs. It performs well in a limited simulation study by WILLIAMS (1991) for over-dispersion models and is easily calculated from the approximate variances and covariances produced by Genstat. Therefore this test was chosen for a first impression of test results for fixed effects in a GLMM model.

In a LMM under normaliy the confidence intervals and the F-test are exact. In a GLMM they are approximate.

In the simulation, to evaluate the coverage probability of the interval for $\gamma$, we only need to check whether the true $\gamma$ is in the interval or not. To this end it is sufficient to check whether the pivotal quantity $Q(\gamma) = \{(\zeta' \hat{W} \hat{e} - \text{RSS})/51\}/\{\text{RSS}/498\}$ is in between the 2.5 and 97.5 percentage points of the F-distribution with degrees of freedom 51 (for classifiers) and 498 (for residual). RSS is the residual sum of squares in an ordinary analysis of variance on $\zeta$ with all effects, including classifiers, entered as fixed effects and with weights $\hat{w}_i$. Weights $\hat{w}_i$ are evaluated for $\hat{\gamma}$, and residuals $\hat{e} = \zeta - X\hat{\theta} - Z\hat{u}$ for the true $\gamma$. For the actual construction of the interval, which is most easily done by plotting $Q$ against $\gamma$, an expression from HARVILLE and FENECH (1985) in terms of eigenvectors and eigenvalues is appropriate. These eigenvectors and eigenvalues have to be calculated only once and apply to all values $\gamma$ considered. The confidence interval for $\phi$ is derived from RSS employing a chi-square distribution with 498 degrees of freedom. The approximate F-test for the hypothesis $\sigma_1^2 = 0$, which is closely connected with the pivotal quantity $Q$, is the F-test for classifiers in the model with fixed classifier effects and residual sum of squares RSS.

### 4.1 *Configurations of parameter values*

The following factors are varied in the simulation:

- The number of batches:
  $N_1$: number $N = 288$, "half" of the original design;
  $N_2$: number $N = 575$, same design as for the actual data.

The design under $N_2$ for the batches is the same with respect to slaughterhouses, experts and classifiers as for the original data. To obtain "half" of this design, for $N_1$ half of the batches were randomly selected from the original design. This new design was used in all simulations involving 288 batches. Due to the random selection of batches, for $N_1$ there is one slaughterhouse less than for $N_2$. Batch sizes were varied under $N_1$ and $N_2$, as shown below, by dividing the original batch sizes by 1, 2, 3, 5 or 10 and rounding to the nearest integer below.

- The batch sizes:
  $B_1$: batch sizes $n/10$ ($\bar{n} = 4.6$);
  $B_2$: batch sizes $n/5$ ($\bar{n} = 9.3$);
  $B_3$: batch sizes $n/3$ ($\bar{n} = 15.0$);
  $B_4$: batch sizes $n/2$ ($\bar{n} = 23.3$);
  $B_5$: batch sizes $n$ from the actual data ($\bar{n} = 46.6$).

Average batch sizes refer to $N_2$. For $N_1$ the average batch sizes for $B_1$ to $B_5$ are 4.7, 9.5, 15.2, 23.7 and 47.5, respectively.

- The component of variance for classifiers:
  $C_1$: $\sigma_1^2 = 0$;
  $C_2$: $\sigma_1^2 = 0.02$ (same order as for the actual data);
  $C_3$: $\sigma_1^2 = 0.2$.

- The fixed effects for experts:
  $F_1$: 0, 0, 0, 0;
  $F_2$: −0.11, −0.05, 0, 0.01 (similar to the actual data);
  $F_3$: −0.22, −0.10, 0, 0.02;
  $F_4$: −0.33, −0.15, 0, 0.03.

The contrast between experts 1 and 4, with values 0, −0.12, −0.24 and −0.36 for $F_1$, $F_2$, $F_3$ and $F_4$ respectively, will be referred to as $c_E$. Estimates and estimated standard errors of this contrast are inspected in the simulation. Slaughterhouse effects are regarded as nuisance parameters, their values are taken from the analysis of the actual data. Pairwise differences between slaughterhouses on the logit scale gradually vary from about 0 to 1.

Configurations are coded with respect to the factors $N$, $B$, $C$ and $F$ and for ease of reference also consecutively numbered in Tables 4, 5 and 6.

### 4.2 *Convergence*

The number of iterations, i.e. repeats of the LMM step, needed to satisfy the convergence criterion, is in most cases less than 10. Worst cases are configurations with classifier component $\sigma_1^2 = 0$ or batch size around 5.

For these configurations the percentage of simulations where the number of iterations exceeds 10 may run to about 15%, with about 3% needing 25 or more interations. For $\sigma_1^2 = 0$, the estimation procedure is slowed down because the optimum is close to or on the boundary; some 60% of the simulations produce a negative estimate for $\sigma_1^2$. For small batch sizes, there is little information in the data about $\sigma_1^2$ and about 25% of the simulations may produce a negative estimate for the classifier component.

### 4.3 *Results for bias*

Table 3 shows estimated bias terms for component $\sigma_1^2$, dispersion parameter $\phi$ and contrast $c_E$ as a percentage of the true value. Also shown are the standard error of the bias percentage (in parentheses) and 0.05 and 0.95 quantiles (between square brackets) of the estimated parameter values, derived from the 1000 simulations.

Table 3

Bias of $\sigma_1^2$, $\phi$ and $c_E$ presented as a percentage of the true value, except when the true value is 0 (underlined). The corresponding standard error is in parentheses. 0.05 and 0.95 quantiles of the estimated values for $\sigma_1^2$, $\phi$ and $c_E$ from the 1000 simulations are between square brackets. The last column shows the percentage of negative estimates for $\sigma_1^2$.

| Conf. nr. | N | B | C | F | $\sigma_1^2$ %bias | (s.e.) | [quantiles] | $\phi$ %bias | (s.e.) | [quantiles] | $c_E$ %bias | (s.e.) | [quantiles] | % comp. neg. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 5 | 3 | 4 | −0.1 | (0.69) | [0.13 ; 0.28 ] | 1.1 | (0.20) | [0.91; 1.11] | 0.47 | (0.41) | [−0.43; −0.28] | 0 |
| 2 | 2 | 5 | 3 | 3 | 0.0 | (0.69) | [0.13 ; 0.28 ] | 1.1 | (0.20) | [0.91; 1.12] | 0.71 | (0.61) | [−0.31; −0.16] | 0 |
| 3 | 2 | 5 | 3 | 2 | 0.0 | (0.69) | [0.13 ; 0.28 ] | 1.3 | (0.20) | [0.91; 1.12] | 1.3 | (1.23) | [−0.20; −0.04] | 0 |
| 4 | 2 | 5 | 3 | 1 | −0.1 | (0.68) | [0.13 ; 0.28 ] | 1.3 | (0.20) | [0.91; 1.12] | 0.0007 | (0.047) | [−0.08; 0.08] | 0 |
| 5 | 2 | 5 | 2 | 4 | 0.7 | (1.02) | [0.01 ; 0.03 ] | 0.6 | (0.20) | [0.90; 1.12] | 0.06 | (0.38) | [−0.43; −0.29] | 0 |
| 6 | 2 | 5 | 2 | 3 | 0.8 | (1.03) | [0.01 ; 0.03 ] | 0.5 | (0.20) | [0.90; 1.12] | 0.25 | (0.58) | [−0.31; −0.17] | 0 |
| 7 | 2 | 5 | 2 | 2 | 0.9 | (1.03) | [0.01 ; 0.03 ] | 0.5 | (0.20) | [0.90; 1.12] | 0.67 | (1.17) | [−0.19; −0.04] | 0 |
| 8 | 2 | 5 | 2 | 1 | 0.9 | (1.03) | [0.01 ; 0.03 ] | 0.4 | (0.20) | [0.90; 1.11] | 0.0011 | (0.045) | [−0.07; 0.07] | 0 |
| 9 | 2 | 5 | 1 | 2 | 0.0006 | (0.0000) | [0.000; 0.033] | 0.3 | (0.20) | [0.90; 1.11] | −0.33 | (1.15) | [−0.19; −0.05] | 66 |
| 10 | 2 | 4 | 3 | 4 | −1.1 | (0.72) | [0.13 ; 0.28 ] | 1.0 | (0.21) | [0.91; 1.12] | 0.92 | (0.61) | [−0.47; −0.24] | 0 |
| 11 | 2 | 4 | 3 | 2 | −1.0 | (0.72) | [0.13 ; 0.28 ] | 1.0 | (0.21) | [0.90; 1.12] | 2.5 | (1.84) | [−0.22; 0.00] | 0 |
| 12 | 2 | 4 | 3 | 1 | −0.9 | (0.72) | [0.13 ; 0.28 ] | 1.0 | (0.21) | [0.91; 1.12] | 0.0019 | (0.002) | [−0.11; 0.12] | 0 |
| 13 | 2 | 4 | 2 | 4 | 0.2 | (1.32) | [0.01 ; 0.03 ] | 0.3 | (0.19) | [0.90; 1.11] | 0.39 | (0.58) | [−0.46; −0.25] | 1 |
| 14 | 2 | 4 | 2 | 2 | 0.7 | (1.31) | [0.01 ; 0.03 ] | 0.2 | (0.19) | [0.90; 1.11] | 1.4 | (1.78) | [−0.22; 0.00] | 1 |
| 15 | 2 | 4 | 2 | 1 | 1.1 | (1.32) | [0.01 ; 0.03 ] | 0.2 | (0.20) | [0.90; 1.11] | 0.0012 | (0.069) | [−0.11; 0.11] | 1 |
| 16 | 2 | 4 | 1 | 2 | 0.0014 | (0.0001) | [0.000; 0.006] | 0.2 | (0.19) | [0.90; 1.10] | 1.6 | (1.72) | [−0.22; −0.01] | 61 |
| 17 | 2 | 3 | 3 | 2 | −0.6 | (0.78) | [0.12 ; 0.28 ] | 1.2 | (0.20) | [0.91; 1.12] | 0.42 | (2.20) | [−0.26; 0.02] | 0 |
| 18 | 2 | 3 | 2 | 2 | −1.4 | (1.63) | [0.00 ; 0.04 ] | 0.6 | (0.19) | [0.91; 1.11] | −1.1 | (2.12) | [−0.25; 0.01] | 3 |
| 19 | 2 | 3 | 1 | 2 | 0.0019 | (0.0001) | [0.000; 0.009] | 0.4 | (0.19) | [0.91; 1.10] | −1.4 | (2.06) | [−0.25; 0.01] | 66 |
| 20 | 2 | 2 | 3 | 4 | −0.6 | (0.84) | [0.12 ; 0.29 ] | 0.6 | (0.19) | [0.91; 1.11] | 1.6 | (0.91) | [−0.53; −0.19] | 0 |
| 21 | 2 | 2 | 3 | 2 | −0.4 | (0.84) | [0.13 ; 0.28 ] | 0.7 | (0.19) | [0.91; 1.12] | 4.1 | (2.80) | [−0.29; −0.06] | 0 |
| 22 | 2 | 2 | 3 | 1 | −0.4 | (0.84) | [0.12 ; 0.30 ] | 0.7 | (0.19) | [0.92; 1.11] | 0.0036 | (0.003) | [−0.17; 0.18] | 0 |
| 23 | 2 | 2 | 2 | 4 | 4.5 | (2.16) | [0.00 ; 0.05 ] | 0.2 | (0.19) | [0.91; 1.11] | 0.44 | (0.87) | [−0.52; −0.19] | 8 |
| 24 | 2 | 2 | 2 | 2 | 5.4 | (2.16) | [0.00 ; 0.05 ] | 0.2 | (0.19) | [0.91; 1.10] | 1.2 | (2.67) | [−0.28; 0.05] | 8 |
| 25 | 2 | 2 | 2 | 1 | 5.5 | (2.17) | [0.00 ; 0.05 ] | 0.2 | (0.19) | [0.91; 1.10] | 0.0028 | (0.003) | [−0.16; 0.17] | 8 |
| 26 | 2 | 2 | 1 | 2 | 0.0033 | (0.0002) | [0.000; 0.015] | 0.2 | (0.19) | [0.91; 1.10] | 0.77 | (2.58) | [−0.28; 0.04] | 63 |
| 27 | 2 | 1 | 3 | 4 | 0.2 | (1.04) | [0.10 ; 0.32 ] | 0.4 | (0.17) | [0.92; 1.09] | 2.2 | (1.29) | [−0.59; −0.10] | 0 |
| 28 | 2 | 1 | 3 | 2 | 0.5 | (1.04) | [0.10 ; 0.32 ] | 0.3 | (0.17) | [0.92; 1.09] | 6.4 | (3.88) | [−0.36; 0.14] | 0 |
| 29 | 2 | 1 | 3 | 1 | 0.4 | (1.04) | [0.10 ; 0.32 ] | 0.3 | (0.17) | [0.92; 1.09] | 0.0068 | (0.005) | [−0.23; 0.25] | 0 |
| 30 | 2 | 1 | 2 | 4 | 14.6 | (3.27) | [0.00 ; 0.06 ] | 0.6 | (0.17) | [0.92; 1.09] | 0.25 | (1.24) | [−0.60; −0.12] | 23 |
| 31 | 2 | 1 | 2 | 2 | 13.5 | (3.30) | [0.00 ; 0.06 ] | 0.4 | (0.17) | [0.91; 1.09] | 2.8 | (3.79) | [−0.36; 0.13] | 25 |
| 32 | 2 | 1 | 2 | 1 | 13.3 | (3.33) | [0.00 ; 0.06 ] | 0.4 | (0.17) | [0.91; 1.09] | 0.0060 | (0.005) | [−0.25; 0.24] | 25 |
| 33 | 2 | 1 | 1 | 2 | 0.0071 | (0.0004) | [0.000; 0.031] | 0.6 | (0.17) | [0.92; 1.10] | 2.8 | (3.72) | [−0.36; 0.11] | 59 |
| 34 | 1 | 4 | 3 | 2 | −0.9 | (0.85) | [0.12 ; 0.30 ] | 1.3 | (0.30) | [0.87; 1.17] | 8.4 | (2.77) | [−0.28; 0.06] | 0 |
| 35 | 1 | 4 | 3 | 1 | −0.9 | (0.85) | [0.12 ; 0.30 ] | 1.4 | (0.30) | [0.86; 1.17] | 0.0101 | (0.003) | [−0.17; 0.19] | 0 |
| 36 | 1 | 4 | 2 | 4 | 2.3 | (1.96) | [0.00 ; 0.04 ] | 0.5 | (0.29) | [0.86; 1.16] | 2.7 | (0.88) | [−0.51; −0.18] | 6 |
| 37 | 1 | 4 | 2 | 2 | 3.1 | (1.95) | [0.00 ; 0.04 ] | 0.4 | (0.29) | [0.86; 1.16] | 8.8 | (2.63) | [−0.27; 0.06] | 6 |
| 38 | 1 | 4 | 2 | 1 | 3.3 | (1.96) | [0.00 ; 0.04 ] | 0.4 | (0.29) | [0.86; 1.16] | 0.0109 | (0.003) | [−0.15; 0.19] | 6 |
| 39 | 1 | 4 | 1 | 2 | 0.0027 | (0.0001) | [0.000; 0.012] | 0.3 | (0.29) | [0.86; 1.15] | 9.4 | (2.54) | [−0.27; 0.05] | 66 |
| 40 | 1 | 4 | 1 | 1 | 0.0027 | (0.0001) | [0.000; 0.012] | 0.3 | (0.29) | [0.86; 1.15] | 0.0116 | (0.003) | [−0.15; 0.18] | 64 |
| 41 | 1 | 3 | 2 | 2 | 1.1 | (2.46) | [0.00 ; 0.05 ] | 0.3 | (0.29) | [0.86; 1.15] | −1.8 | (3.09) | [−0.31; 0.07] | 15 |
| 42 | 1 | 2 | 2 | 2 | 16.6 | (3.54) | [0.00 ; 0.07 ] | 0.7 | (0.30) | [0.87; 1.18] | 2.5 | (4.24) | [−0.39; 0.14] | 28 |
| 43 | 1 | 1 | 3 | 2 | 1.2 | (1.43) | [0.07 ; 0.36 ] | 0.7 | (0.26) | [0.88; 1.15] | 10.3 | (5.98) | [−0.50; 0.26] | 1 |
| 44 | 1 | 1 | 3 | 1 | 1.2 | (1.45) | [0.06 ; 0.37 ] | 0.7 | (0.26) | [0.87; 1.15] | 0.0149 | (0.007) | [−0.36; 0.41] | 0 |
| 45 | 1 | 1 | 2 | 2 | 49.3 | (5.42) | [0.00 ; 0.10 ] | 1.2 | (0.27) | [0.88; 1.16] | 13.8 | (6.03) | [−0.49; 0.27] | 39 |
| 46 | 1 | 1 | 2 | 1 | 47.9 | (5.31) | [0.00 ; 0.10 ] | 1.2 | (0.27) | [0.88; 1.16] | 0.0209 | (0.007) | [−0.37; 0.42] | 37 |
| 47 | 1 | 1 | 1 | 2 | 0.0136 | (0.0007) | [0.00 ; 0.06 ] | 1.3 | (0.27) | [0.87; 1.16] | 13.8 | (6.01) | [−0.48; 0.28] | 62 |
| 48 | 1 | 1 | 1 | 1 | 0.0135 | (0.0007) | [0.00 ; 0.06 ] | 1.3 | (0.26) | [0.88; 1.15] | 0.0215 | (0.007) | [−0.34; 0.40] | 61 |

Results for $N_2$ (575 batches) are shown in the top half of the table. Only for small batch sizes and small component $\sigma_1^2$ for classifiers, the percentage bias in $\hat{\sigma}_1^2$ is sizeable, in all other cases the bias is negligible. The larger bias percentages go together with high probabilities for a negative estimate for the classifier component, as shown in the last column of the table. For instance in configuration 31 the estimated probability for a negative estimate is 0.25. But even for this configuration, where the estimated percentage bias is 13.5%, the estimates are hardly misleading since the corresponding standard errors (see Table 4 discussed below) are of the same order as the estimates, reflecting the fact that the data convey little information about the component. Although the bias for $c_E$ runs to 6.4% for configuration 28, none of the estimated bias terms is significantly different from zero.

For $N_1$ (288 batches) for small batch size and small classifier component, large bias in $\hat{\sigma}_1^2$ is found. For configuration 45 the classifier component is over-estimated by a factor of almost 1.5. The estimated probability for a negative estimate for $\sigma_1^2$ is 0.39 for this configuration. For larger batch sizes, e.g. in configuration 37, bias is small. Bias for $c_E$ is appreciable and runs to some 14% for the smaller batch sizes. However, this is the same order of bias as for ordinary logistic regression for data configurations such as these. Configuration 39 for instance, shows an estimated bias percentage of 9.4 (2.54) %, while ordinary logistic regression on the same data, ignoring classifiers, yields a similar estimated bias of 9.8 (2.54) %.

Although the bias in $\phi$, for some configurations, is significantly different from 0, it is negligible in all cases studied. An alternative estimator for $\phi$ is SSR divided by the appropriate number of degrees of freedom for $N_1$ and $N_2$. Results for this estimator are similar to those reported in Table 3.

### 4.4 *Results for standard errors of estimates*

Table 4 shows the standard errors of the estimates as derived from the 1000 simulations. These standard errors are referred to as the "empirical" standard errors. Also shown are the mean and 0.05 and 0.95 quantiles of the standard errors produced by Genstat in the 1000 simulations.

Observe that for $N_2$ the mean standard error for $\phi$ produced by Genstat is similar to the value $\sqrt{(2/498)} = 0.0634$ based on a chi-square distribution with 498 degrees of freedom. For decreasing batch sizes, the standard error tends to be over-estimated. For small batch sizes the chi-square approximation becomes less appropriate (asymptotics are with respect to $n \to \infty$); the true distribution is somewhat shorter tailed. However, the estimated 0.05 and 0.95 quantiles in Table 3 are about 0.92 and 1.09 and quite similar to the values 0.90 and 1.11 for the $\chi^2_{498}/498$ distribution, as derived with the Wilson-Hilferty approximation (ABRAMOWITZ and STEGUN, 1965, 26.4.14, p. 941). For $N_1$ the standard error based on a chi-square distribution with 212 degrees of freedom is 0.0971 and the quantiles are 0.85 and 1.16. It seems that a size 0.05 test for over- or underdispersion, employing a chi-square approximation, would not do too badly; it tends to be somewhat conservative.

Table 4

Standard errors of estimates. The "true" (empirical) standard error from the 1000 simulations and the mean and 0.05 and 0.95 quantiles of the estimated standard errors produced by Genstat.

| Conf. | | | | | $\sigma_1^2$ | | | $\phi$ | | | $c_E$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| nr. | N | B | C | F | emp. | mean | [quantiles] | emp. | mean | [quantiles] | emp. | mean | [quantiles] |
| 1 | 2 | 5 | 3 | 4 | 0.0436 | 0.0435 | [0.030; 0.059] | 0.0644 | 0.0641 | [0.058; 0.071] | 0.0462 | 0.0474 | [0.045; 0.050] |
| 2 | 2 | 5 | 3 | 3 | 0.0435 | 0.0435 | [0.030; 0.059] | 0.0647 | 0.0641 | [0.057; 0.071] | 0.0464 | 0.0475 | [0.044; 0.050] |
| 3 | 2 | 5 | 3 | 2 | 0.0434 | 0.0435 | [0.030; 0.059] | 0.0644 | 0.0641 | [0.057; 0.070] | 0.0468 | 0.0479 | [0.045; 0.051] |
| 4 | 2 | 5 | 3 | 1 | 0.0432 | 0.0435 | [0.030; 0.059] | 0.0641 | 0.0641 | [0.057; 0.071] | 0.0470 | 0.0483 | [0.045; 0.051] |
| 5 | 2 | 5 | 2 | 4 | 0.0065 | 0.0064 | [0.004; 0.009] | 0.0644 | 0.0634 | [0.057; 0.070] | 0.0434 | 0.0454 | [0.043; 0.048] |
| 6 | 2 | 5 | 2 | 3 | 0.0065 | 0.0064 | [0.004; 0.009] | 0.0647 | 0.0633 | [0.057; 0.070] | 0.0438 | 0.0455 | [0.043; 0.048] |
| 7 | 2 | 5 | 2 | 2 | 0.0065 | 0.0065 | [0.004; 0.009] | 0.0644 | 0.0633 | [0.057; 0.070] | 0.0443 | 0.0458 | [0.043; 0.048] |
| 8 | 2 | 5 | 2 | 1 | 0.0065 | 0.0064 | [0.004; 0.009] | 0.0641 | 0.0633 | [0.057; 0.070] | 0.0449 | 0.0461 | [0.044; 0.048] |
| 9 | 2 | 5 | 1 | 2 | 0.0010 | 0.0017 | [0.001; 0.002] | 0.0632 | 0.0624 | [0.056; 0.069] | 0.0437 | 0.0437 | [0.041; 0.046] |
| 10 | 2 | 5 | 3 | 4 | 0.0457 | 0.0462 | [0.031; 0.063] | 0.0652 | 0.0639 | [0.057; 0.071] | 0.0695 | 0.0669 | [0.063; 0.071] |
| 11 | 2 | 4 | 3 | 2 | 0.0456 | 0.0462 | [0.032; 0.063] | 0.0652 | 0.0639 | [0.057; 0.071] | 0.0700 | 0.0675 | [0.063; 0.071] |
| 12 | 2 | 4 | 3 | 1 | 0.0457 | 0.0463 | [0.032; 0.063] | 0.0657 | 0.0639 | [0.057; 0.071] | 0.0709 | 0.0681 | [0.064; 0.072] |
| 13 | 2 | 4 | 2 | 4 | 0.0084 | 0.0083 | [0.005; 0.011] | 0.0614 | 0.0631 | [0.057; 0.069] | 0.0665 | 0.0636 | [0.060; 0.067] |
| 14 | 2 | 4 | 2 | 2 | 0.0083 | 0.0083 | [0.005; 0.012] | 0.0614 | 0.0630 | [0.056; 0.069] | 0.0676 | 0.0642 | [0.061; 0.067] |
| 15 | 2 | 4 | 2 | 1 | 0.0083 | 0.0084 | [0.005; 0.012] | 0.0618 | 0.0630 | [0.056; 0.069] | 0.0682 | 0.0647 | [0.061; 0.068] |
| 16 | 2 | 4 | 1 | 2 | 0.0022 | 0.0035 | [0.003; 0.005] | 0.0611 | 0.0623 | [0.056; 0.069] | 0.0652 | 0.0620 | [0.059; 0.065] |
| 17 | 2 | 3 | 3 | 2 | 0.0496 | 0.0494 | [0.034; 0.067] | 0.0628 | 0.0640 | [0.058; 0.071] | 0.0835 | 0.0838 | [0.079; 0.089] |
| 18 | 2 | 3 | 2 | 2 | 0.0103 | 0.0102 | [0.006; 0.015] | 0.0606 | 0.0631 | [0.057; 0.070] | 0.0803 | 0.0794 | [0.075; 0.083] |
| 19 | 2 | 3 | 1 | 2 | 0.0033 | 0.0054 | [0.004; 0.007] | 0.0590 | 0.0625 | [0.057; 0.069] | 0.0780 | 0.0773 | [0.074; 0.081] |
| 20 | 2 | 2 | 3 | 4 | 0.0529 | 0.0540 | [0.037; 0.074] | 0.0602 | 0.0636 | [0.058; 0.070] | 0.1039 | 0.1047 | [0.099; 0.110] |
| 21 | 2 | 2 | 3 | 2 | 0.0530 | 0.0541 | [0.037; 0.074] | 0.0606 | 0.0636 | [0.058; 0.070] | 0.1062 | 0.1057 | [0.100; 0.112] |
| 22 | 2 | 2 | 3 | 1 | 0.0529 | 0.0541 | [0.037; 0.075] | 0.0603 | 0.0636 | [0.058; 0.070] | 0.1061 | 0.1066 | [0.101; 0.113] |
| 23 | 2 | 2 | 2 | 4 | 0.0136 | 0.0137 | [0.008; 0.020] | 0.0599 | 0.0628 | [0.057; 0.069] | 0.0990 | 0.0992 | [0.095; 0.104] |
| 24 | 2 | 2 | 2 | 2 | 0.0137 | 0.0137 | [0.008; 0.020] | 0.0595 | 0.0627 | [0.057; 0.069] | 0.1014 | 0.1002 | [0.095; 0.105] |
| 25 | 2 | 2 | 2 | 1 | 0.0137 | 0.0138 | [0.008; 0.020] | 0.0595 | 0.0627 | [0.057; 0.069] | 0.1028 | 0.1010 | [0.096; 0.106] |
| 26 | 2 | 2 | 1 | 2 | 0.0056 | 0.0087 | [0.007; 0.012] | 0.0597 | 0.0623 | [0.057; 0.068] | 0.0977 | 0.0982 | [0.093; 0.103] |
| 27 | 2 | 1 | 3 | 4 | 0.0661 | 0.0654 | [0.043; 0.092] | 0.0533 | 0.0632 | [0.058; 0.069] | 0.1468 | 0.1468 | [0.143; 0.156] |
| 28 | 2 | 1 | 3 | 2 | 0.0657 | 0.0656 | [0.043; 0.091] | 0.0525 | 0.0632 | [0.058; 0.069] | 0.1471 | 0.1500 | [0.143; 0.157] |
| 29 | 2 | 1 | 3 | 1 | 0.0655 | 0.0656 | [0.043; 0.091] | 0.0532 | 0.0632 | [0.058; 0.069] | 0.1463 | 0.1511 | [0.144; 0.159] |
| 30 | 2 | 1 | 2 | 4 | 0.0207 | 0.0225 | [0.015; 0.033] | 0.0541 | 0.0628 | [0.057; 0.068] | 0.1411 | 0.1414 | [0.135; 0.148] |
| 31 | 2 | 1 | 2 | 2 | 0.0209 | 0.0224 | [0.015; 0.033] | 0.0537 | 0.0627 | [0.057; 0.068] | 0.1437 | 0.1428 | [0.137; 0.149] |
| 32 | 2 | 1 | 2 | 1 | 0.0210 | 0.0225 | [0.015; 0.033] | 0.0537 | 0.0627 | [0.057; 0.068] | 0.1457 | 0.1440 | [0.137; 0.151] |
| 33 | 2 | 1 | 1 | 2 | 0.0118 | 0.0178 | [0.015; 0.025] | 0.0542 | 0.0626 | [0.057; 0.068] | 0.1411 | 0.1414 | [0.135; 0.148] |
| 34 | 1 | 4 | 3 | 2 | 0.0536 | 0.0528 | [0.035; 0.074] | 0.0937 | 0.0969 | [0.083; 1.111] | 0.1051 | 0.1066 | [0.098; 0.115] |
| 35 | 1 | 4 | 3 | 1 | 0.0535 | 0.0529 | [0.036; 0.074] | 0.0941 | 0.0970 | [0.083; 1.112] | 0.1062 | 0.1075 | [0.100; 0.116] |
| 36 | 1 | 4 | 2 | 4 | 0.0124 | 0.0122 | [0.007; 0.017] | 0.0903 | 0.0946 | [0.081; 0.108] | 0.1002 | 0.0979 | [0.091; 0.105] |
| 37 | 1 | 4 | 2 | 2 | 0.0124 | 0.0122 | [0.007; 0.017] | 0.0901 | 0.0945 | [0.081; 0.109] | 0.0999 | 0.0989 | [0.092; 0.106] |
| 38 | 1 | 4 | 2 | 1 | 0.0124 | 0.0123 | [0.007; 0.018] | 0.0903 | 0.0945 | [0.081; 0.108] | 0.1009 | 0.0997 | [0.093; 0.107] |
| 39 | 1 | 4 | 1 | 2 | 0.0046 | 0.0071 | [0.006; 0.010] | 0.0907 | 0.0930 | [0.080; 0.107] | 0.0965 | 0.0960 | [0.090; 0.103] |
| 40 | 1 | 4 | 1 | 1 | 0.0045 | 0.0071 | [0.006; 0.010] | 0.0903 | 0.0929 | [0.080; 0.107] | 0.0979 | 0.0969 | [0.090; 0.104] |
| 41 | 1 | 3 | 2 | 2 | 0.0156 | 0.0159 | [0.010; 0.024] | 0.0909 | 0.0940 | [0.081; 0.107] | 0.1172 | 0.1222 | [0.113; 0.131] |
| 42 | 1 | 2 | 2 | 2 | 0.0224 | 0.0229 | [0.015; 0.035] | 0.0936 | 0.0941 | [0.081; 0.109] | 0.1608 | 0.1550 | [0.144; 0.167] |
| 43 | 1 | 1 | 3 | 2 | 0.0907 | 0.0881 | [0.055; 0.126] | 0.0831 | 0.0953 | [0.083; 0.108] | 0.2271 | 0.2332 | [0.217; 0.250] |
| 44 | 1 | 1 | 3 | 1 | 0.0918 | 0.0882 | [0.054; 0.126] | 0.0836 | 0.0953 | [0.083; 0.108] | 0.2306 | 0.2351 | [0.219; 0.252] |
| 45 | 1 | 1 | 2 | 2 | 0.0343 | 0.0416 | [0.030; 0.061] | 0.0848 | 0.0941 | [0.082; 0.108] | 0.2289 | 0.2223 | [0.208; 0.238] |
| 46 | 1 | 1 | 2 | 1 | 0.0336 | 0.0416 | [0.030; 0.060] | 0.0854 | 0.0941 | [0.082; 0.108] | 0.2328 | 0.2243 | [0.209; 0.241] |
| 47 | 1 | 1 | 1 | 2 | 0.0226 | 0.0363 | [0.029; 0.051] | 0.0847 | 0.0938 | [0.081; 0.107] | 0.2280 | 0.2208 | [0.205; 0.237] |
| 48 | 1 | 1 | 1 | 1 | 0.0225 | 0.0364 | [0.029; 0.050] | 0.0831 | 0.0938 | [0.082; 0.106] | 0.2294 | 0.2228 | [0.207; 0.239] |

When the true value of $\sigma_1^2$ is zero, which is on the boundary of the parameter space, standard errors derived from Fisher information are not appropriate, see e.g. configuration 9. Since the estimated standard errors for the contrast $c_E$ do not account for variability in the estimates for $\sigma_1^2$ and $\phi$, they were expected to be smaller than the empirical values, but this is not always the case. Differences are small.

By and large, the correspondence between the empirical standard errors and the standard errors produced by Genstat, is quite satisfactory.

### 4.5 *Results for significance tests and confidence intervals*

As an additional check on the usefulnes of the standard error of $\hat{c}_E$, say $s_E$, as produced by Genstat, the coverage probability of the approximate 0.95 confidence interval $(\hat{c}_E - 1.96\ s_E;\ \hat{c}_E + 1.96\ s_E)$ was estimated from the 1000 simulations. Coverage probabilities were also estimated for the approximate 0.95 confidence intervals for $\gamma$ and $\phi$. Estimated coverage probabilities, and power and size of the Wald test for experts and approximate F-test for classifiers are shown in Table 5

Table 5

Coverage probabilities of approximate 0.95 confidence intervals for $c_E$, $\gamma$ and $\phi$. Size/power of Wald test for experts and F-test for classifiers.

| Conf. | | | | | Coverage probabilities of confidence intervals | | | Power or size of | |
|---|---|---|---|---|---|---|---|---|---|
| nr. | N | B | C | F | $c_E$ | $\gamma$ | $\phi$ | Wald test for experts | F-test for classifiers |
| 1 | 2 | 5 | 3 | 4 | 0.955 | 0.950 | 0.951 | 1.000 | 1.000 |
| 2 | 2 | 5 | 3 | 3 | 0.957 | 0.951 | 0.948 | 1.000 | 1.000 |
| 3 | 2 | 5 | 3 | 2 | 0.957 | 0.956 | 0.951 | 0.571 | 1.000 |
| 4 | 2 | 5 | 3 | 1 | 0.957 | 0.953 | 0.955 | 0.051 | 1.000 |
| 5 | 2 | 5 | 2 | 4 | 0.961 | 0.951 | 0.943 | 1.000 | 0.997 |
| 6 | 2 | 5 | 2 | 3 | 0.962 | 0.952 | 0.938 | 1.000 | 0.998 |
| 7 | 2 | 5 | 2 | 2 | 0.963 | 0.955 | 0.939 | 0.637 | 0.998 |
| 8 | 2 | 5 | 2 | 1 | 0.960 | 0.954 | 0.946 | 0.050 | 0.999 |
| 9 | 2 | 5 | 1 | 2 | 0.956 | 0.939 | 0.948 | 0.678 | 0.042 |
| 10 | 2 | 4 | 3 | 4 | 0.939 | 0.952 | 0.941 | 0.999 | 1.000 |
| 11 | 2 | 4 | 3 | 2 | 0.945 | 0.956 | 0.938 | 0.327 | 1.000 |
| 12 | 2 | 4 | 3 | 1 | 0.949 | 0.950 | 0.939 | 0.049 | 0.949 |
| 13 | 2 | 4 | 2 | 4 | 0.947 | 0.952 | 0.954 | 0.999 | 0.947 |
| 14 | 2 | 4 | 2 | 2 | 0.946 | 0.952 | 0.952 | 0.366 | 0.954 |
| 15 | 2 | 4 | 2 | 1 | 0.938 | 0.952 | 0.952 | 0.050 | 0.958 |
| 16 | 2 | 4 | 1 | 2 | 0.935 | 0.950 | 0.957 | 0.381 | 0.058 |
| 17 | 2 | 3 | 3 | 2 | 0.953 | 0.945 | 0.949 | 0.210 | 1.000 |
| 18 | 2 | 3 | 2 | 2 | 0.947 | 0.958 | 0.963 | 0.233 | 0.784 |
| 19 | 2 | 3 | 1 | 2 | 0.949 | 0.941 | 0.967 | 0.246 | 0.049 |

Table 5 (continued)

| Conf. nr. | N | B | C | F | Coverage probabilities of confidence intervals $c_E$ | $\gamma$ | $\phi$ | Power or size of Wald test for experts | F-test for classifiers |
|---|---|---|---|---|---|---|---|---|---|
| 20 | 2 | 2 | 3 | 4 | 0.953 | 0.958 | 0.955 | 0.870 | 1.000 |
| 21 | 2 | 2 | 3 | 2 | 0.945 | 0.961 | 0.961 | 0.145 | 1.000 |
| 22 | 2 | 2 | 3 | 1 | 0.950 | 0.958 | 0.955 | 0.040 | 1.000 |
| 23 | 2 | 2 | 2 | 4 | 0.950 | 0.945 | 0.966 | 0.901 | 0.539 |
| 24 | 2 | 2 | 2 | 2 | 0.951 | 0.946 | 0.967 | 0.165 | 0.538 |
| 25 | 2 | 2 | 2 | 1 | 0.946 | 0.950 | 0.966 | 0.053 | 0.542 |
| 26 | 2 | 2 | 1 | 2 | 0.943 | 0.950 | 0.965 | 0.166 | 0.056 |
| 27 | 2 | 1 | 3 | 4 | 0.948 | 0.949 | 0.978 | 0.548 | 0.999 |
| 28 | 2 | 1 | 3 | 2 | 0.951 | 0.955 | 0.978 | 0.095 | 0.998 |
| 29 | 2 | 1 | 3 | 1 | 0.960 | 0.947 | 0.976 | 0.041 | 0.998 |
| 30 | 2 | 1 | 2 | 4 | 0.945 | 0.948 | 0.973 | 0.602 | 0.254 |
| 31 | 2 | 1 | 2 | 2 | 0.940 | 0.947 | 0.974 | 0.114 | 0.256 |
| 32 | 2 | 1 | 2 | 1 | 0.946 | 0.945 | 0.977 | 0.052 | 0.254 |
| 33 | 2 | 1 | 1 | 2 | 0.947 | 0.950 | 0.974 | 0.105 | 0.056 |
| 34 | 1 | 4 | 3 | 2 | 0.945 | 0.921 | 0.935 | 0.114 | 1.000 |
| 35 | 1 | 4 | 3 | 1 | 0.948 | 0.914 | 0.929 | 0.052 | 1.000 |
| 36 | 1 | 4 | 2 | 4 | 0.939 | 0.916 | 0.937 | 0.898 | 0.622 |
| 37 | 1 | 4 | 2 | 2 | 0.942 | 0.915 | 0.937 | 0.149 | 0.617 |
| 38 | 1 | 4 | 2 | 1 | 0.939 | 0.915 | 0.930 | 0.061 | 0.626 |
| 39 | 1 | 4 | 1 | 2 | 0.952 | 0.920 | 0.928 | 0.147 | 0.053 |
| 40 | 1 | 4 | 1 | 1 | 0.942 | 0.926 | 0.925 | 0.062 | 0.057 |
| 41 | 1 | 3 | 2 | 2 | 0.961 | 0.926 | 0.939 | 0.124 | 0.384 |
| 42 | 1 | 2 | 2 | 2 | 0.941 | 0.918 | 0.923 | 0.100 | 0.249 |
| 43 | 1 | 1 | 3 | 2 | 0.961 | 0.927 | 0.953 | 0.055 | 0.926 |
| 44 | 1 | 1 | 3 | 1 | 0.943 | 0.923 | 0.953 | 0.036 | 0.924 |
| 45 | 1 | 1 | 2 | 2 | 0.939 | 0.929 | 0.933 | 0.055 | 0.129 |
| 46 | 1 | 1 | 2 | 1 | 0.948 | 0.920 | 0.938 | 0.039 | 0.134 |
| 47 | 1 | 1 | 1 | 2 | 0.939 | 0.930 | 0.942 | 0.056 | 0.043 |
| 48 | 1 | 1 | 1 | 1 | 0.939 | 0.934 | 0.947 | 0.037 | 0.040 |

Overall, the standard error $s_E$ gives a fair impression of the accuracy of $\hat{c}_E$, as judged from the coverage probabilities of the simple normal approximation confidence interval. Coverage probabilities for $\phi$ for $N_2$ for smaller batch sizes tend to be rather high, e.g. 0.978 for configuration 28, in agreement with the corresponding estimated standard errors being too high in Table 4. For $N_1$ the coverage probabilities for $\gamma$ are appreciably lower than 0.95. Estimated sizes of the Wald and F-test are reasonably close to 0.05. The power of the F-test for a small classifier component $\sigma_1^2 = 0.02$ is moderate to high for batch sizes around 25 or 15, but is considerably reduced for batch sizes around 10 or 5, where the discrete nature of the data is becoming more pronounced.

Overall, the procedures for confidence intervals and significance tests as developed for ordinary LMMs, when applied to the adjusted dependent variate, appear to perform well enough for practical use.

## 5. Discussion

Formally the mixed model on the logit scale may be derived following SCHEFFÉ (1959, Chap. 8). For details see ENGEL and BUIST (1993).

With $c_{ij}$ the total random contribution to the linear predictor for the $i$-th expert and $j$-th classifier, the covariance matrix $\Sigma = (\sigma_{ii'})$ of the independent vectors $(c_{1j}, c_{2j}, c_{3j}, c_{4j})'$ is assumed to have the simple form: $\sigma_{ii} = \sigma^2$ and $\sigma_{ii'} = \varrho\sigma^2$, $i \neq i'$, with $0 \leqq \varrho \leqq 1$. Since experts are supposed to be similar with respect to classification this is not an unreasonable assumption. In contrast to SCHEFFÉ (1959, Chap. 8), random effects are introduced without side conditions, as has become customary in unbalanced mixed models, see SEARLE et al. (1992, p. 123–127).

The estimation procedure, although presented for a logistic regression model with components of variance, applies to a variety of GLMMs, as will be clear from the general notation. All calculations can be performed with standard software available for ordinary LMMs. If necessary, e.g. for binary data, the dispersion factor $\phi$ can be fixed at value 1 (Genstat offers an option to do so).

From (4) it can be shown that at convergence the following equations are solved:

$$\begin{aligned} X' \hat{W}(g'(\mu) \odot (y - \mu)) &= 0, \\ Z' \hat{W}(g'(\mu) \odot (y - \mu)) &= \phi G^{-1} u, \end{aligned} \tag{5}$$

where $\odot$ denotes the elementwise product (Hadamard product). Equations (5) are similar to the QL equations for fixed $u$ (with appropriate side conditions) except for the term $\phi G^{-1} u$ on the right hand side. It easily follows that (5) may be obtained by putting first derivatives with respect to elements of $\beta$ and $u$ of $D + u' G^{-1} u$ equal to zero, where $D$ is the quasi-deviance conditional upon $u$ and $u' G^{-1} u$ acts as a penalty function for the random effects. When the distribution of $y$ conditional upon $u$ is in the GLM exponential family, for normal random effects, minimization of the penalized quasi-deviance is equivalent to maximization of the joint probability density function of $y$ and $u$, similar to REML in a LMM.

Large sample properties of the estimation procedure should be derived from the estimating equations (3) and (4) or (3) and (5). The asymptotics for QL (MCCULLAGH, 1983) and MINQUE (BROWN, 1976), cover some cases for "large" samples and "small" components of variance. See also MILLER (1977). Genstat produces large sample approximations for variances and covariances of estimators based on Fisher information under the assumption of normality. At least for small-dispersion asymptotics, e.g. large binomial totals or large Poisson

means, under normality assumptions for the additional random effects, these approximations will behave as for ordinary mixed models.

It should be possible to relax normality assumptions for these approximations to hold. However, results with respect to unbiasedness of the estimates and predictions from (4) (KACKAR and HARVILLE, 1981) show that symmetry of the distribution of the random effects in the linear predictor is a desirable feature. Furthermore, for realistic sample sizes, the random effects should probably have small kurtosis.

Since MINQUE and I-MINQUE use error contrasts (see SEARLE et al., 1992, Chap. 12) they should have less bias in the variance components estimates than ML under full distributional assumptions, e.g. binomial or Poisson distributions combined with additional normal random effects in the linear predictor. No attempt is made to tackle the estimating equations analytically, but the simulation results promote confidence in the usefulness of the estimation procedure and further inference based on the approximate LMM for the adjusted dependent variate.

We will briefly discuss some alternatives to ML presented in the literature, in relation to the extended IRLS method presented in this paper. In GIANOLA and FOULLEY (1983) a Bayesian procedure is presented for threshold models for ordered categorical data in animal breeding. An equivalent approach is presented in HARVILLE and MEE (1984). Restricting attention to binomial data, the threshold model is a particular instance of a GLMM. The link function follows from the "residual" probability distribution of the "liability", e.g. the standard logistic distribution corresponds to the logit link and the standard normal distribution to the probit link. Parameter $\phi$ should be fixed at value 1. Estimating equations in GIANOLA and FOULLEY (GF) and HARVILLE and MEE (HM) may be shown to be the same as those in ENGEL and KEEN (1994) (EK) and in this paper. Algorithms of GF/HM and EK notably differ with respect to the way components of variance are updated. In EK MINQUE leads to a Fisher scoring update, while in GF/HM a normal approximation of the posterior distribution of the random effects leads to an update resembling the EM algorithm for LMMs. The latter algorithm is considerably slower than the former. SCHALL (1991) proposes two algorithms for GLMMs mimicking the ML and REML EM algorithms for LMMs. The REML type algorithm, say SREML, is equivalent to GF/HM. A penalized quasi-likelihood (PQL) method based on LaPlacean integration, proposed by BRESLOW and CLAYTON (1993), although derived by quite a different line of argumentation, is equivalent to EK, both with respect to the estimating equations as with respect to the algorithm suggested. Estimation in MCGILCHRIST (1994) is based on maximization of the joint probability density function of $y$ and $u$. Consequently, under the assumption stated below (5), this is equivalent to the approach illustrated in this paper with respect to $\beta$ and $u$. The REML type estimators for the components of variance in MCGILCHRIST (1994) are of the same form as the EM type updates in SREML and GF/HM. In GILMOUR et al. (1985), in the context of a threshold model for binomial data with

a probit link and normal random effects, a QL method (GAR) is proposed which is different from the methods discussed above. Rather than using conditional moments, as in EK, marginal moments are used, integrating out the random effects. Where $\zeta$ in EK is formulated in terms of conditional moments, the adjusted dependent variate of GAR is expressed in terms of marginal moments. The marginal quasi-likelihood method presented in BRESLOW and CLAYTON (1993) is a generalisation of GAR.

The major difference between the methods discussed lies in the use of either conditional or marginal moments with respect to the random effects. Simulation for a simple sire model with small family sizes in GILMOUR et al. (1985) suggests that GAR has smaller bias for estimated heritability than GF/HM (and consequently also SREML, PQL and EK).

Heritability, for e.g. a sire model, is defined as $4\sigma_1^2/(\sigma_1^2+\tau^2)$, where $\sigma_1^2$ is the sire component and $\tau^2=\pi^2/3$ for the standard logistic and $\tau^2=1$ for the standard normal distribution.

GF/HM is biased downward. Simulation results in HOESCHELE and GIANOLA (1988) however, for a more complex sire model, suggest that GF/HM performs better than GAR, both with respect to bias and mean squared error. For both methods heritability estimates are severely biased upward. The average progeny group size in HOESCHELE and GIANOLA (1988) is 40 and the sire variance for the liability, for the standard logistic distribution, rather than the standard normal distribution, is about 0.2. This is in the order of the average number of carcasses of about 50 per classifier and $\sigma_1^2=0.2$ for $B_5$ and $C_1$ in Table 3. However, in Table 3 serious overestimation for $\sigma_1^2$ only occurs for the smaller number of units and the smaller value of 0.02 for the component in configurations 42, 45 and 46. The positive bias for these configurations seems to be related to the active non-negativity constraint on the component. Configurations referred to as D1 in BRESLOW and CLAYTON (1993) contain one component of variance and are to some extent comparable with a simple sire scheme and the simulation study in this paper. The component is equal to 1 and "family sizes" vary from 7 to 56, with a non trivial design for the fixed effects. PQL tends to underestimate the variance component.

The suggestion from the simulation results produced sofar is that in those cases where there is little or modest information on most of the individual random effects, GF/HM/SREML/PQL/EK has a tendency to overshrink these effects. In a simple sire scheme this would happen when e.g. family sizes are small. For small components and small binomial totals, the non-negativity constraints on the components become "active" and may be a source of positive bias. Since results in GILMOUR et al. (1985), BRESLOW and CLAYTON (1993) and the present paper do not seem to agree with HOESCHELE and GIANOLA (1988), further simulation is needed, especially for areas of research such as animal breeding where components of variance and prediction of random effects are of first interest. Presently, work is in progress on an application of GLMMs to

threshold models for binary data for birth difficulties with sheep and we hope to get a clearer impression of the performance of EK and GAR from simulation on the basis of that data.

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# Chapter 6

## Inference for threshold models with variance components from the generalized linear mixed model perspective

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Application of IRREML to threshold models for binary data. Threshold models for binary data are a sub-class of the class of GLMMs. Simulation results indicate that for binary data estimators for variance components may be severely biased. Contrary to other studies reported in the literature, it is found that bias is not necessarily negative.

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**Original article**

# Inference for threshold models with variance components from the generalized linear mixed model perspective

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**Summary** – The analysis of threshold models with fixed and random effects and associated variance components is discussed from the perspective of generalized linear mixed models (GLMMs). Parameters are estimated by an interative procedure, referred to as iterated re-weighted REML (IRREML). This procedure is an extension of the iterative re-weighted least squares algorithm for generalized linear models. An advantage of this approach is that it immediately suggests how to extend ordinary mixed-model methodology to GLMMs. This is illustrated for lambing difficulty data. IRREML can be implemented with standard software available for ordinary normal data mixed models. The connection with other estimation procedures, eg, the maximum *a posteriori* (MAP) approach, is discussed. A comparison by simulation with a related approach shows a distinct pattern of the bias of MAP and IRREML for heritability. When the number of fixed effects is reduced, while the total number of observations is kept about the same, bias decreases from a large positive to a large negative value, seemingly independently of the sizes of the fixed effects.

**binomial data / threshold model / variance components / generalized linear model / restricted maximum likelihood**

**Résumé – Inférence sur les composantes de variance des modèles à seuil dans une perspective de modèle linéaire mixte généralisé.** *L'analyse des modèles à seuils avec effets fixes et aléatoires et des composantes de variance correspondantes est ici placée dans la perspective des modèles linéaires mixtes généralisés (GLMMs). Les paramètres sont estimés par une procédure itérative, appelée maximum de vraisemblance restreinte repondéré obtenu par itération (IRREML). Cette procédure est une extension de l'algorithme itératif des moindres carrés repondérés pour les modèles linéaires généralisés. Elle a l'avantage de suggérer immédiatement une manière d'étendre la méthodologie habituelle du modèle mixte aux GLMMs. Une application à des données de difficultés d'agnelage est présentée. IRREML peut être mis en œuvre avec les logiciels standard disponibles pour les modèles linéaires mixtes normaux habituels. Le lien avec d'autres procédures d'estimation, par exemple l'approche du maximum* a posteriori *(MAP), est discuté. Une comparaison*

*par simulation avec une méthode voisine montre un biais caractéristique du MAP et de l'IRREML pour l'héritabilité. Quand le nombre des effets fixés est diminué, à nombre total d'observations constant, le biais passe d'une valeur fortement positive à une valeur fortement négative, apparemment indépendantes de l'importance des effets fixés.*

**distribution binomiale / modèle à seuil / composante de variance / modèle linéaire généralisé / maximum de vraisemblance restreinte**

## INTRODUCTION

In his paper on sire evaluation Thompson (1979) already pointed out the potential interest for binomial data in modifying the generalized linear model (GLM) estimating equations to allow for random effects. He conjectured that if modification is feasible, generalization towards other distributions such as the Poisson or gamma distribution should be easy. The iterated re-weighted restricted maximum likelihood (IRREML) procedure (Schall, 1991; Engel and Keen, 1994) for generalized linear mixed models (GLMM) proves to be exactly such a modification. IRREML is motivated by the fact that in GLMMs the adjusted dependent variate in the iterated re-weighted least squares (IRLS) algorithm (McCullagh and Nelder, 1989, § 2.5) approximately follows an ordinary mixed-model structure with weights for the residual errors and, in the absence of under- or overdispersion, residual error variance fixed at a constant value (typically 1). IRREML is quite flexible and not only covers a variety of underlying distributions for the threshold model but also easily extends to other types of data such as count data, for example, litter size. This entails simple changes in the algorithm with respect to link and variance function employed. When the residual error variance for the adjusted dependent variate is not fixed, it represents an additional under- or overdispersion parameter which is a useful feature, for example, under- or overdispersed Poisson counts. Calculations in this paper are performed with REML (Patterson and Thompson, 1971) facilities for ordinary mixed models in Genstat 5 (1993). Software for animal models such as DFREML (Meyer, 1989), after some modification, can be used for IRREML as well.

Methods for inference in ordinary normal data mixed models, *eg*, the Wald test (Cox and Hinkley, 1974, p 323) for fixed effects, are also potentially useful for GLMMs, as will be illustrated for the lambing difficulty data. Simulation results for the Wald test in a GLMM for (overdispersed) binomial data were presented in Engel and Buist (1995).

For threshold models with normal underlying distributions and known components of variance, Gianola and Foulley (1983) observe that their Bayesian maximum *a posteriori* (MAP) approach produces estimating equations for fixed and random effects such as those anticipated by Thompson. Under normality assumptions, for fixed components of variance, IRREML will be shown to be equivalent to MAP. IRREML therefore offers an alternative, non-Bayesian, derivation of MAP. The MAP approach was also presented in Harville and Mee (1984), including estimation of variance components. Their updates of the components of variance are akin to those of the estimation maximization (EM) algorithm (Searle *et al*, 1992, § 8.3) for REML. The algorithm presented in Engel and Keen (1994), which is used in this

paper, is related to Fisher scoring. Both algorithms solve the same final estimating equations, but the latter is considerably faster than the former.

Gilmour *et al* (1985) presented an iterative procedure for threshold models with normal underlying distributions, which also uses an adjusted dependent variate and residual weights. This approach, which will be referred to as GAR, is different from MAP and IRREML. In the terminology of Zeger *et al* (1988) MAP and IRREML are closely related to the subject-specific nature of the GLMM, while GAR is of a population-averaged nature, as will be explained in more detail in this paper.

A number of authors, *eg*, Preisler (1988), Im and Gianola (1988), and Jansen (1992), have discussed maximum likelihood estimation for threshold models. Apart from the fact that straightforward maximum likelihood estimation does not correct for loss of degrees of freedom due to estimation of fixed effects, as REML does in the conventional mixed model, it is also handicapped by the need for high-dimensional numerical integration. Maximum likelihood estimation for models with several components of variance, especially with crossed random effects, is practically impossible. IRREML is more akin to quasi-likelihood estimation (McCullagh and Nelder, 1989, chap 9; McCullagh, 1991): conditional upon the random effects only; the relationship between the first 2 moments is employed while no full distributional assumptions are needed beyond existence of the first 4 moments.

Since practical differences between various methods proposed pertain mainly to their subject-specific or population-averaged nature, we will give some attention to a comparison between GAR and IRREML. Simulation studies were reported in Gilmour *et al* (1985), Breslow and Clayton (1993), Hoeschele and Gianola (1989), and Engel and Buist (1995). Conclusions from the Hoeschele and Gianola study differ from conclusions from the other studies with respect to bias of MAP/IRREML and GAR. Since the Hoeschele and Gianola study was rather modest in size, it was decided to repeat it here in more detail, *ie* under a variety of parameter configurations and for larger numbers of simulations.

## GLMMs and threshold models

### *The GLMM model*

Suppose that random effects are collected in a random vector $\mathbf{u}$, with zero means and dispersion matrix $\mathbf{G}$, *eg*, for a sire model $\mathbf{G} = \mathbf{A}\sigma_s^2$, where $\mathbf{A}$ is the additive relationship matrix and $\sigma_s^2$ the sire component of variance. Conditional upon $\mathbf{u}$, *eg*, for given sires, observations $y$ are assumed independent, with variances proportional to known functions $V$ of the means $\mu$:

$$\mathrm{E}(y|u) = \mu \quad \text{and} \quad \mathrm{Var}(y|u) = \phi\, V(\mu) \qquad [1]$$

For binary data, $y = 1$ may denote a difficult birth and $y = 0$ a normal birth. The mean $\mu$ is the probability of a difficult birth for offspring of a particular sire. The conditional variance is $\mathrm{Var}(y|u) = V(\mu) = \mu(1-\mu)$ and $\phi$ equals 1. For proportions $y = x/n$, an appropriate choice may be:

$$\mathrm{Var}(y|u) = \phi V(\mu) = \phi\mu(1-\mu)/n \qquad [2]$$

Parameter $\phi$ may be included to allow for under- or overdispersion relative to binomial variation (McCullagh and Nelder, 1989, § 4.5). Observe that [2] is inappropriate when $n$ is predominantly small or large: for $n = 1$ no overdispersion is possible and $\phi$ should equal 1 and for $n \rightarrow \infty$, [2] vanishes to 0 while extra-binomial variation should remain. More complicated variances (Williams, 1982) may be obtained by replacing $\phi$ in [1] by $\{1 + (n-1)\sigma_0^2\}$ or by $\{1 + (n-1)\sigma_0^2\mu(1-\mu)\}$. In both expressions $\sigma_0^2$ is a variance corresponding to a source of overdispersion (for a discussion of underdispersion see Engel and Te Brake, 1993). Limits for $n \rightarrow \infty$ of the variances are $\sigma_0^2\mu(1-\mu)$ and $\sigma_0^2\mu^2(1-\mu)^2$, respectively. Both can be accomodated in a GLMM for continuous proportions, *eg*, motility of spermatozoa, and are covered by IRREML.

The mean $\mu$ is related to a linear predictor $\eta$ by means of a known link function $g$: $\eta = g(\mu)$. The linear predictor is a combination of fixed and random effects: $\eta = \mathbf{x}'\boldsymbol{\beta} + \mathbf{z}'\mathbf{u}$, where $\mathbf{x}$ and $\mathbf{z}$ are design vectors for fixed and random effects collected in vectors $\boldsymbol{\beta}$ and $\mathbf{u}$, respectively. For difficulty of birth, for instance, $\eta$ may include main effects for parity of the dam and a covariable for birthweight as fixed effects and the genetic contribution of the sire as a random effect. Popular link functions for binary or binomial data are the logit and probit link functions: $\text{logit}(\mu) = \log(\mu/(1-\mu)) = \eta$ and $\text{probit}(\mu) = \Phi^{-1}(\mu) = \eta$, where $\Phi^{-1}$ is the inverse of the cumulative density function (cdf) of the standard normal distribution.

### *The threshold model*

Suppose that $r$ is the 'liability', an underlying random variable such that $y = 1$ when $r$ exceeds a threshold value $\theta$ and $y = 0$ otherwise. Without loss of generality it may be assumed that $\theta = 0$. Let $\eta$ be the mean of $r$, conditional upon $u$. Furthermore, let the cdf of the residual $\varepsilon = (r - \eta)$, say $F$, be independent of $u$. Then

$$\mu = P(y = 1|u) = P(r > 0|u) = 1 - F(-\eta) \quad \text{and so} \quad \eta = -F^{-1}(1-\mu)$$

where $F^{-1}$ is the inverse of $F$. It follows that the threshold model is a GLMM with link function $g(\mu) = -F^{-1}(1-\mu)$, which simplifies to $g(\mu) = F^{-1}(\mu)$ when $\varepsilon$ is symmetrically distributed. Residual $\varepsilon$ may represent variation due to Mendelian sampling and environment. Probabilities $\mu$ do not change when $r$ is multiplied by an arbitrary positive constant and the variance of $\varepsilon$ can be fixed at any convenient constant value, say $\sigma^2$. When $F$ is the cdf $L$ of the standard logistic distribution, *ie* $F(\varepsilon) = L(\varepsilon) = 1/(1 + \exp(-\varepsilon))$, $g$ is the logit link and $\sigma^2 = \pi^2/3$. When $F$ is the cdf $\Phi$ of the standard normal distribution, $g$ will be the probit link and $\sigma^2 = 1$. Although the logistic distribution has relatively longer tails than the normal distribution, to a close approximation (Jonhson and Kotz, 1970, p 6):

$$\Phi(t) = L(ct) \qquad [3]$$

where $c = (15/16)\pi/\sqrt{3}$. Results of analyses with a probit or logit link are usually virtually equivalent, apart from the scaling factor $c$ for the effects and $c^2$ for the components of variance. Heritability may be defined on the liability scale, *eg*, for a sire model: $h^2 = 4\sigma_s^2/(\sigma_s^2 + \sigma^2)$. As a function of $\sigma_s^2/\sigma^2$ heritability does not depend on the choice of $\sigma^2$. Hence, estimates $\widehat{h^2}$ for the probit and logit link are often about the same.

### *Conditional and marginal effects*

In a GLMM, effects are introduced in the link-transformed conditional means, *ie* in the linear predictor $\eta = g(\mu)$. Consequently, effects refer to subjects or individuals. The GLMM and the threshold model are both subject-specific models, using the terminology of Zeger *et al* (1988). This is in contrast with a population-averaged model where effects are introduced in the link-transformed marginal means $g(E(\mu))$ and refer to the population as a whole. In animal breeding, where sources of variation have a direct physical interpretation and are of primary interest, a subject-specific model, which explicitly introduces these sources of variation through random effects, seems the natural choice. For fixed effects however, presentation in terms of averages over the population is often more appropriate. In the threshold model, there is no information in the data about the phenotypic variance of the liability, allowing $\sigma^2$ to be fixed at an arbitrary value. Intuitively one would expect the expressions for marginal effects to involve some form of scaling by the underlying phenotypic standard deviation. For normally distributed random effects and probit link this is indeed so. From $r \sim N(\mathbf{x}'\boldsymbol{\beta},\ \mathbf{z}'\mathbf{G}\mathbf{z} + 1)$ the marginal probability, say $p$, follows directly:

$$p = P(y = 1) = P(r > 0) = \Phi(\mathbf{x}'\boldsymbol{\beta}(\mathbf{z}'\mathbf{G}\mathbf{z} + 1)^{-0.5})$$

Hence, the probit link also holds for marginal probabilities, but the effects are shrunken by a factor $\lambda_p = (\mathbf{z}'\mathbf{G}\mathbf{z}+1)^{-0.5}$. For a sire model $\lambda_p = (\sigma_s^2+1)^{-0.5}$. That the same link applies for both conditional means $\mu$ and marginal means $p$ is rather exceptional. For the logit link, the exact integral expression for $p$ cannot be reduced to any simple form (Aitchison and Shen, 1980). However, from [3] it follows that the logit link holds approximately for $p$, with shrinkage factor $\lambda_L = ((\mathbf{z}'\mathbf{G}\mathbf{z}/c^2)+1)^{-0.5}$. Without full distributional assumptions, for relatively small components of variance, marginal moments may also be obtained by a Taylor series expansion (see Engel and Keen, 1994).

Binary observations $y_i$ and $y_j$ corresponding to, for instance, the same sire will be correlated. For the probit link the covariance follows from:

$$\begin{aligned}\mathrm{cov}(y_i,\ y_j) &= E_u(\mathrm{cov}(y_i,\ y_j|u)) + \mathrm{cov}_u(E(y_i|u),\ E(y_j|u)) = \mathrm{cov}_u(\mu_i,\ \mu_j)\\ &= E_u[P(r_i > 0,\ r_j > 0|u)] - p_i p_j = P(r_i > 0,\ r_j > 0) - p_i p_j\\ &= \Phi_2(\lambda_p \mathbf{x}_i'\boldsymbol{\beta},\ \lambda_p \mathbf{x}_j'\boldsymbol{\beta};\ \rho_{ij}) - p_i p_j \qquad [4]\end{aligned}$$

Here $\Phi_2(a, b;\ \rho)$ is the cdf of the bivariate normal distribution with zero means, unit variances and correlation coefficient $\rho$, $\rho_{ij}$ is the correlation on the underlying scale, *eg*, in a simple sire model $\rho_{ij} = \sigma_s^2/(\sigma_s^2 + 1)$. For the logit link, using [3], $\lambda_p$ should be replaced by $\lambda_L/c$, while the value of the correlation, expressed in terms of the components of variance in the logit model, is about the same. The double integral in $\Phi_2$ may effectively be reduced to a single integral (Sowden and Ashford, 1969), which can be evaluated by Gauss quadrature (Abramowitz and Stegun, 1965, p 924). Alternatively, for small $\rho^2$, a Taylor expansion (Pearson, 1901; Abramowitz

and Stegun, 1965, 26.3.29, p 940) may be used:

$$\Phi_2(a,b;\,\rho) = \Phi(a)\Phi(b) + \tau(a)\tau(b)\rho + \sum_{t=1}^{\infty} \tau^{(t)}(a)\tau^{(t)}(b)\rho^{t+1}/(t+1)! \qquad [5]$$

where $\tau^{(t)}$ is the $t$th derivative of the probability density function (pdf) $\tau$ of the standard normal distribution. For a sire model, under normality assumptions, the first-order approximation appears to be satisfactory, except for extreme incidence rates $p$ (Gilmour *et al*, 1985). By grouping of $n$ binary observations pertaining to the same fixed and random effect, moments for binomial proportions $y$ immediately follow from [4], *eg*:

$$\mathrm{Var}(y) = p(1-p)[1 + (n-1)\{\Phi_2(\lambda_p \mathbf{x}'\boldsymbol{\beta},\ \lambda_p \mathbf{x}'\boldsymbol{\beta};\ \rho) - p^2\}/p(1-p)]/n \qquad [6]$$

where $\rho$ is the intra-class correlation on the liability scale. Expression [6] can be simplified by using [5]. Results for the logit link follow from [3].

## Estimation of parameters

### *The algorithm for IRREML*

The algorithm will be described briefly. For details see Engel and Keen (1994) and Engel and Buist (1993a). Suppose that $\boldsymbol{\beta}_0$ and $\mathbf{u}_0$ are starting values obtained from an ordinary GLM fit with, for example, random effects treated as if they were fixed or with random effects ignored, *ie* $\mathbf{u}_0 = 0$. After the initial GLM has been fitted by IRLS, the adjusted dependent variate $\zeta$ and iterative weights $w$ (McCullagh and Nelder, 1989, § 2.5) are saved:

$$\zeta = (y - \mu_0)g'(\mu_0) + g(\mu_0) \quad \text{and} \quad w = \{g'(\mu_0)^2 V(\mu_0)\}^{-1} \qquad [7]$$

where $g'$ is the derivative of the link function with respect to $\mu$, *eg*, for the probit link: $w = n\tau(\eta_0)^2/\{\mu_0(1-\mu_0)\}$, $\zeta$ approximately follows an ordinary mixed-model structure with weights $w$ for the residual errors and residual variance $\phi$. Now a minimum norm quadratic unbiased estimation (MINQUE) (Rao, 1973, § 4j) is applied to $\zeta$, employing the Fisher scoring algorithm for REML (1 step of this algorithm corresponds to MINQUE). From the mixed-model equations (MMEs) (Henderson, 1963; Searle *et al*, 1992, § 7.6) new values $\widehat{\boldsymbol{\beta}}$ and $\widehat{\mathbf{u}}$ for the fixed and random effects are solved:

$$\begin{bmatrix} \mathbf{X}'\mathbf{W}\mathbf{X} & \mathbf{X}'\mathbf{W}\mathbf{Z} \\ \mathbf{Z}'\mathbf{W}\mathbf{X} & \mathbf{Z}'\mathbf{W}\mathbf{Z} + \phi\mathbf{G}^{-1} \end{bmatrix} \begin{bmatrix} \boldsymbol{\beta} \\ \mathbf{u} \end{bmatrix} = \begin{bmatrix} \mathbf{X}'\mathbf{W}\zeta \\ \mathbf{Z}'\mathbf{W}\zeta \end{bmatrix}$$

Here, $\mathbf{X}$ and $\mathbf{Z}$ are the design matrices for the fixed and random effects respectively, $\mathbf{W}$ is a diagonal matrix with weights $w$ along the diagonal and $\zeta$ denotes the vector of values of the adjusted dependent variate. $\boldsymbol{\beta}_0$ and $\mathbf{u}_0$ are replaced by $\widehat{\boldsymbol{\beta}}$ and $\widehat{\mathbf{u}}$, $\zeta$ and $w$ are updated and a new MINQUE step is performed. This is repeated until convergence. Note that MINQUE does not require full

distributional assumptions beyond the existence of the first 4 moments and may be presented as a weighted least-squares method (Searle *et al*, 1992, Ch 12).

### *Some properties of IRREML*

When the MMEs are expressed in terms of the original observations $y$, it is readily shown that at convergence the following equations are solved:

$$\begin{aligned}\mathbf{X}'\widehat{\mathbf{W}}(g'(\boldsymbol{\mu})^*(\mathbf{y}-\boldsymbol{\mu})) &= 0,\\ \mathbf{Z}'\widehat{\mathbf{W}}(g'(\boldsymbol{\mu})^*(\mathbf{y}-\boldsymbol{\mu})) &= \phi\ \mathbf{G}^{-1}\mathbf{u}\end{aligned} \qquad [8]$$

where * denotes a direct elementwise (Hadamard) product. These equations are similar to the GLM equations for fixed $\mathbf{u}$ (with appropriate side conditions) except for the term $\phi\ \mathbf{G}^{-1}\mathbf{u}$ on the right-hand side. Equations [8] may also be obtained by setting first derivatives with respect to elements of $\boldsymbol{\beta}$ and $\mathbf{u}$ of $D + \mathbf{u}'\mathbf{G}^{-1}\mathbf{u}$ equal to zero, where $D$ is the (quasi) deviance (see McCullagh and Nelder, 1989, § 2.3 and § 9.2.2.) conditional upon $\mathbf{u}$. The assumption of randomness for $\mathbf{u}$ imposes a 'penalty' on values which are 'too far' from 0. When the pdf of observations $\mathbf{y}$ conditional upon normally distributed random effects $\mathbf{u}$ is in the GLM exponential family, *eg*, a binomial or Poisson distribution, maximization of $D+\mathbf{u}'\mathbf{G}^{-1}\mathbf{u}$ is easily shown to be equivalent to maximization of the joint pdf of $\mathbf{y}$ and $\mathbf{u}$.

Suppose that we have a sire model with $q$ sires and sire variance component $\sigma_s^2$. The IRREML estimating equations for $\sigma_s^2$ and $\phi$ (see, for example, Engel, 1990) are:

$$\text{trace}(\mathbf{Z}_k'\mathbf{P}\mathbf{Z}_k\mathbf{A}_k) = \boldsymbol{\zeta}'\mathbf{P}\mathbf{Z}_k\mathbf{A}_k\mathbf{Z}_k'\mathbf{P}\boldsymbol{\zeta},\ k = 0,\ 1 \qquad [9]$$

Here $\mathbf{Z}_0 = \mathbf{I}$, $\mathbf{Z}_1$ is the design matrix for the sires, $\mathbf{A}_0 = \mathbf{W}^{-1}$, $\mathbf{A}_1 = \mathbf{A}$, $\mathbf{P} = \Omega^{-1} - \Omega^1\mathbf{X}(\mathbf{X}'\Omega^{-1}\mathbf{X})^{-1}\mathbf{X}'\Omega^{-1}$ and $\Omega = \mathbf{Z}\mathbf{G}\mathbf{Z}' + \phi\mathbf{W}^{-1}$. The difference with ordinary REML equations is that $\boldsymbol{\zeta}$ depends on the parameter values as well. The MINQUE/Fisher scoring update of IRREML can be recovered from [9], by using $\mathbf{P} = \mathbf{P}\Omega\mathbf{P} = \sigma_s^2\mathbf{P}\mathbf{Z}_1\mathbf{A}\mathbf{Z}_1'\mathbf{P} + \phi\mathbf{P}\mathbf{W}^{-1}\mathbf{P}$ on the left-hand side:

$$\sum_k \text{trace}(\mathbf{Z}_{k'}'\mathbf{P}\mathbf{Z}_k\mathbf{A}_k\mathbf{Z}_k'\mathbf{P}\mathbf{Z}_{k'}\mathbf{A}_{k'})\sigma_k^2 = \boldsymbol{\zeta}'\mathbf{P}\mathbf{Z}_{k'}\mathbf{A}_{k'}\mathbf{Z}_{k'}'\mathbf{P}\boldsymbol{\zeta},\ k' = 0,\ 1 \qquad [10]$$

where $\sigma_0^2 = \phi$ and $\sigma_1^2 = \sigma_s^2$. When $\phi$ is fixed at value 1, the equation for $k' = 0$ is dropped from [10]. Alternative updates related to the EM algorithm may also be obtained from [9] (see, for example, Engel, 1990), and will be of interest when other estimation procedures are discussed:

$$\widehat{\sigma}_s^2 = \{\widehat{\mathbf{u}}'\mathbf{A}^{-1}\widehat{\mathbf{u}} + \text{trace}(\mathbf{A}^{-1}\mathbf{T})\}/q \qquad [11]$$

Here $\mathbf{T}/\phi$ is the part of the inverse of the MME coefficient matrix corresponding to $\mathbf{u}$.

With quasi-likelihood (QL) for independent data, it is suggested (McCullagh and Nelder, 1989, § 4.5 and chap 9) that one can estimate $\phi$ from Pearson's (generalized) chi-square statistic. From [9] it may be shown that $\widehat{\phi} = X_p^2/d$, where $X_p^2 = \sum_j (y_j - \widehat{\mu}_j)^2/V(\widehat{\mu}_j)$ is Pearson's chi-square in terms of conditional means and

variances and $d = N - \text{rank}(\mathbf{X}) - \{q - \text{trace}(\mathbf{A}^{-1}\mathbf{T}/\widehat{\sigma}_s^2)\}$ is an associated 'number of degrees of freedom'.

## Application to birth difficulties in sheep

The data are part of a study into the scope for a Texel sheep breeding program in the Netherlands employing artificial insemination. Lambing difficulty will be analyzed as a binary variable: 0 for a normal birth and 1 for a difficult birth. There are 43 herd-year-season (HYS) effects. Herds are nested within regions and regions are nested within years. There are 2 years, 3 regions per year, about 4 herds per region, and 3 seasons. The 33 sires are nested within regions. The 433 dams are nested within herds with about 20 dams per herd. Observations are available from 674 offspring of the sires and dams.

Variability on the liability scale may depend on litter size. Therefore, observations corresponding to a litter size of 1 and litter sizes of 2 or more are analyzed separately. Corresponding data sets are referred to as the S-set (single; 191 observations) and M-set (multiple; 483 observations). The M-set is reproduced in Engel and Buist (1993) and is available from the authors. Some summary statistics are shown in table I.

**Table I.** Summary statistics for the lambing difficulty data and 'raw' fractions for difficult births and corresponding numbers of progeny for the S- and M-set.

| | *S-set* | | *M-set* | |
|---|---|---|---|---|
| | *Mean* | *Number of progeny* | *Mean* | *Number of progeny* |
| Year 1 | 0.76 | 59 | 0.50 | 204 |
| Year 2 | 0.84 | 132 | 0.77 | 279 |
| Season 1 | 0.78 | 93 | 0.64 | 286 |
| Season 2 | 0.83 | 84 | 0.71 | 180 |
| Season 3 | 0.93 | 14 | 0.41 | 17 |
| Overall | 0.82 | 191 | 0.66 | 483 |

Table II shows some results for components of variance, for models fitted to the S- and M-sets. Dam effects are absorbed. To stabilize convergence, the occurrence of extreme weights was prevented by limiting fitted values on the probit scale to the range $[-3.5, 3.5]$. In addition to fixed HYS effects, factors for age and parity of the dam ($P$), sex of the lamb ($S$), and for the M-set a covariate for litter size ($L$ = litter size – 2) and included. Levels for factor $P$ consist of the following 6 combinations of age and parity: (1;1), (2;1), (2;2), (3; $\leqslant$ 2), (4; $\geqslant$ 3) and ($\geqslant$ 5; $\geqslant$ 4). In models 3, 4 and 5 a factor $D$ for pelvic dimension of the dam ('wide', 'normal' or 'narrow'), and in models 4 and 5 a covariate $W$ = birthweight – average birthweight of the lamb is also included, with separate averages of 4.27 and 3.63 for the S- and M-sets respectively.

Fixed effects may be screened by applying the Wald test to the values of $\zeta$ saved from the last iteration step. Some results for the M-set are shown in

**Table II.** Estimated components of variance $\sigma_S^2$ and $\sigma_D^2$ for sires and dams, $h^2 = 4\sigma_S^2/(1+\sigma_S^2+\sigma_D^2)$, $\rho = \sigma_D^2/(1+\sigma_S^2+\sigma_D^2)$.

| | $\sigma_S^2$ | $\sigma_D^2$ | $h^2$ | $\rho$ |
|---|---|---|---|---|
| *S-set, model* | | | | |
| 1. HYS + S + P | 0.25 (0.30) | | 0.81 (0.79) | |
| 2. HY + S + P | 0.13 (0.21) | | 0.46 (0.66) | |
| 3. HY + S + P + D | 0.09 (0.24) | | 0.34 (0.81) | |
| 4. HY + S + P + D + W | 0.10 (0.29) | | 0.38 (0.95) | |
| 5. HY + S + P + D + W + D × W | 0.01 (0.26) | | 0.04 (1.00) | |
| *M-set, model* | | | | |
| 1. HYS + S + P + L + S × L | 0.00 ( − ) | 0.84 (0.25) | 0.00 ( − ) | 0.46 (0.07) |
| 2. HY + S + P + L + S × L | 0.00 ( − ) | 0.69 (0.20) | 0.00 ( − ) | 0.41 (0.07) |
| 3. HY + S + P + L + S × L + D | 0.00 ( − ) | 0.69 (0.21) | 0.00 ( − ) | 0.41 (0.07) |
| 4. HY + S + P + L + S × L + D + W | 0.01 (0.09) | 0.71 (0.22) | 0.02 (0.21) | 0.42 (0.07) |
| 5. HY + S + P + L + S × L + D + W + D × W | 0.00 (0.09) | 0.74 (0.22) | 0.00 (0.21) | 0.43 (0.07) |

Standard errors are in parentheses. S, P and D denote main effects, W and L are covariables, S × L and D × W are interactions. When an estimate is negative (−), the component is assumed to be negligible and set to 0.

table III. In all cases, test statistics are calculated for the values of the variance components obtained for the corresponding full model, *ie* model 1–5. Variability due to estimation of the variance components is ignored. For each line in the table the corresponding test statistic accounts for effects above that line, but ignores effects below the line. Referring to a chi-square distribution, in model 1 seasonal effects seem to be unimportant and are excluded from the subsequently fitted models.

In model 3 for the M-set, the following contrasts for pelvic opening ($D$) are found: 0.520 (0.231), 2.019 (0.547) and 1.499 (0.531), for 'normal' *versus* 'wide', 'narrow' *versus* 'wide' and 'narrow' *versus* 'normal', respectively. Pairwise comparison, with a normal approximation, shows that any 2 levels are significantly ($P < 0.05$) different. The effects refer to the probits of the conditional probabilities. For the probits of the marginal probabilities, effects have to be multiplied by $(1+\sigma_S^2+\sigma_D^2)^{-0.5} = 0.769$ (from table II). The difference between 'narrow' and 'wide', for example, becomes 1.55 (0.43). In model 5 for the M-set, separate coefficients for birthweight are fitted for the 3 levels of pelvic opening. The estimated coefficient for birthweight for a dam with a narrow pelvic opening is 0.72 (0.61); this is about 0.47 (0.63) higher than the estimates for the other 2 levels, which are about the same. Although a larger coefficient is to be expected for a narrow pelvic opening, the difference found is far from significant. Fitting a common coefficient, *ie* dropping the interaction $D \times W$ between pelvic opening and birthweight in model 4, gives an estimated coefficient for birthweight of 0.28 (0.15), which becomes 0.21 (0.12) after shrinkage. By comparison, the coefficient for the S-set, after shrinkage, is 0.92 (0.30). The reduced effect of birthweight for the M-set agrees with the negligible values found for the component of variance for sires.

**Table III.** Some test results for the fixed effects for the M-set.

**A**

| | *Wald statistics Model 1* | *Degrees of freedom* |
|---|---|---|
| S = sex of lamb | 0.4 | 1 |
| P = parity / age of dam | 2.8 | 5 |
| L = litter size | 2.2 | 1 |
| S × L | 0.1 | 1 |
| *HYS* | | |
| Years | 18.0* | 1 |
| Seasons | 0.9 | 2 |
| Years × Regions | 20.0* | 4 |
| Years × Seasons | 1.0 | 2 |
| Years × Regions × Herds | 29.1* | 16 |
| Years × Regions × Seasons | 1.3 | 5 |
| Years × Regions × Seasons × Herds | 4.4 | 12 |

**B**

| | *Wald statistics* | | | | *Degrees* |
|---|---|---|---|---|---|
| | *Model 2* | *Model 3* | *Model 4* | *Model 5* | *of freedom* |
| Years | 18.7* | 18.0* | 16.2* | 16.7* | 1 |
| Years × Regions | 21.8* | 22.6* | 21.8* | 22.0* | 4 |
| Years × Regions × Herds | 46.5* | 39.7* | 37.6* | 37.5* | 16 |
| S = sex of lamb | 3.0 | 2.6 | 2.7 | 2.7 | 1 |
| P = parity/age of dam | 7.2 | 5.6 | 5.5 | 5.4 | 5 |
| D (pelvic opening) | – | 15.6* | 14.6* | 13.0* | 2 |
| L = litter size | 2.5 | 2.3 | 2.1 | 2.1 | 1 |
| W (birth weight lamb) | – | – | 3.3 | 3.2 | 1 |
| S × L | 0.1 | 0.0 | 0.0 | 0.0 | 1 |
| D × W | – | – | – | 0.6 | 2 |

* $P < 0.05$, referring to a chi-square distribution, ignoring effects in the following rows.

## Relation to other methods

We will mainly concentrate on differences between GAR and IRREML. GAR is based on QL for the marginal moments with a probit link and normally distributed random effects (see also Foulley *et al*, 1990). QL-estimating equations for dependent data are (McCullagh and Nelder, 1989, § 9.3): $\mathbf{D}'\text{Var}(\mathbf{y})^{-1}\ (\mathbf{y} - \mathbf{p}) = \mathbf{0}$, where the matrix of derivatives $\mathbf{D} = (d_{ij})$, $d_{ij} = (\partial p_i/\partial \beta_{*j})$, follows from $\mathbf{p} = \Phi(\mathbf{X}\boldsymbol{\beta}_*)$, and $\boldsymbol{\beta}_* = \lambda_p \boldsymbol{\beta}$ denotes the vector of marginal fixed effects. It follows from [6] that:

$$\text{Var}(\mathbf{y}) = \mathbf{R} + \mathbf{B}(\mathbf{Z}\mathbf{C}\mathbf{Z}')\mathbf{B}' + 0(\rho^2) \qquad [12]$$

where $\mathbf{R} = \text{diag}(\{p(1-p) - \rho\tau^2(\lambda_p \mathbf{X}\boldsymbol{\beta})\}/n)$, $\mathbf{B} = \text{diag}(\tau(\lambda_p \mathbf{X}\boldsymbol{\beta}))$, $\mathbf{C} = \lambda_p^2 \mathbf{G}$ and $\rho$ represents the appropriate intraclass correlation. Var($\mathbf{y}$) will be replaced by [12], ignoring terms of order $\rho^2$ and higher. The QL equations may be solved by iterated generalized least squares on an adjusted dependent variate, say $\zeta_{\text{GAR}}$:

$$\zeta_{\text{GAR}} = \mathbf{X}\widehat{\boldsymbol{\beta}}_* + \widehat{\mathbf{B}}^{-1}(\mathbf{y} - \widehat{\mathbf{p}}) = \mathbf{X}\widehat{\boldsymbol{\beta}}_* + \text{diag}(\tau(\mathbf{X}\widehat{\boldsymbol{\beta}}_*))^{-1}\ (\mathbf{y} - \widehat{\mathbf{p}})$$

where $\widehat{\mathbf{B}}$ is $\mathbf{B}$ evaluated at $\widehat{\boldsymbol{\beta}}_*$. By comparison, the adjusted dependent variate from [7] is:

$$\zeta = \mathbf{X}\widehat{\boldsymbol{\beta}} + \mathbf{Z}\widehat{\mathbf{u}} + \text{diag}(\tau(\mathbf{X}\widehat{\boldsymbol{\beta}} + \mathbf{Z}\widehat{\mathbf{u}}))^{-1}\ (\mathbf{y} - \widehat{\boldsymbol{\mu}})$$

The latter variate relates to a first-order approximation of the conditional means $\mu$, while the former relates to a first-order approximation of the marginal means $p$. Approximately $\text{Var}(\zeta_{\text{GAR}}) = \widehat{\mathbf{B}}^{-1}\text{Var}(\mathbf{y})\widehat{\mathbf{B}}^{-1} = \widehat{\mathbf{B}}^{-1}\mathbf{R}\widehat{\mathbf{B}}^{-1} + \mathbf{ZCZ}' = \mathbf{W}_{\text{GAR}}^{-1} + \mathbf{ZCZ}'$, and Gilmour *et al* (1985) solve MMEs in terms of $\zeta_{\text{GAR}}$ and $\mathbf{W}_{\text{GAR}}$. For example, in a sire model with $q$ sires, predictions from these MMEs for $\lambda_p \mathbf{u}$, say $\widehat{\mathbf{u}}_{\text{GAR}}$, are used to update the intraclass correlation $\rho$. Analogous to [11] with $\phi = 1$:

$$\widehat{\rho}_{\text{GAR}} = \{\widehat{\mathbf{u}}'_{\text{GAR}}\mathbf{A}^{-1}\widehat{\mathbf{u}}_{\text{GAR}} + \text{trace}(\mathbf{A}^{-1}\mathbf{T}_{\text{GAR}})\}/q \qquad [3]$$

Both GAR and IRREML are based on an approximate mixed-model structure for an adjusted dependent variate. Note however that in GAR, in contrast to IRREML, predictions of the random effects are only used to update the components of variance and do not enter $\mathbf{W}_{\text{GAR}}$ and $\zeta_{\text{GAR}}$ directly. At the end of this section we shall see that this may be an advantage for GAR over IRREML in situations where there is little information in the data about individual random effects, *eg*, in a sire scheme with small family sizes or extreme incidence. The marginal quasi-likelihood method (MQL) presented in Breslow and Clayton (1993) can be regarded as a generalization of GAR. However, in its more general setting, MQL does not have the benefit of some of the exact results for binomial data and underlying normal distributions used to derive GAR.

In MAP, assuming a vague prior for $\boldsymbol{\beta}$ and a normal prior for $\mathbf{u}$, the posterior mean for $(\boldsymbol{\beta}', \mathbf{u}')'$ is approximated by the posterior mode. Hence, $(\widehat{\boldsymbol{\beta}}', \widehat{\mathbf{u}}')'$ maximize the joint pdf of $\mathbf{y}$ and $\mathbf{u}$. Under normality this is equivalent to maximization of a penalized deviance. Hence, the estimating equations for $\boldsymbol{\beta}$ and $\mathbf{u}$ for MAP and IRREML are the same and given by [8]. As shown in Foulley *et al* (1987) an estimator for, for instance, a sire component $\sigma_S^2$, may be solved from: $E_0[\partial/\partial\sigma_S^2 \log(f(\mathbf{u}|\sigma_S^2))] = 0$. Here, $f(.|.)$ denotes a (conditional) pdf for the variables indicated, and expectation $E_0$ is with respect to $f(\mathbf{u}|\mathbf{y}, \sigma_S^2)$. The latter pdf may be approximated by a normal density with mean $\widehat{\mathbf{u}}$ and dispersion $\mathbf{T}$. In an iterative scheme this leads to the EM-type update [11]. Consequently, MAP and IRREML also solve the same final estimating equations with respect to the components of variance, although the algorithms used are different.

The penalized quasi-likelihood method (PQL) presented in Breslow and Clayton (1993) is based on Laplace integration. Random effects are assumed to be normally distributed. The log pdf of $\mathbf{y}$ conditional upon $\mathbf{u}$ is replaced by a quasi-likelihood. When parameter $\phi$ is involved, the extended quasi-likelihood (Nelder and Pregibon,

1987) can be used, see Engel and Buist (1993). In the resulting integral expression, the logarithm of the integrand in terms of $\mathbf{u}$ is approximated by a quadratic function around its optimum in $\widehat{\mathbf{u}}$, employing expected second-order derivatives. Now random effects are easily integrated out. Some further approximations, *eg*, approximating conditional deviance residuals by Pearson residuals, result in a normal log likelihood for the adjusted dependent variate $\zeta$ from [7]. An REML type adjustment for loss of degrees of freedom due to estimation of fixed effects finally yields an REML log likelihood, which is maximized by Fisher scoring. Hence, although motivated quite differently, PQL is equivalent to IRREML (for details see Engel and Buist, 1993).

A comparison between GAR and MAP/PQL/IRREML by simulation was presented in Gilmour *et al* (1985). They consider a simple one-way model, *eg*, a sire model with $q$ unrelated sires, with $n$ offspring per sire, and with a binary observation per offspring. An overall mean is the only fixed effect. Gilmour *et al* (1985) observe that there is a tendency for MAP/PQL/IRREML to underestimate $h^2$ for small family size $n$ or extreme incidence $p$. For extreme incidence $p$, GAR tends to overestimate $h^2$. As also noted by Thompson (1990), for this simple set-up, closed-form expressions can be derived from [8] and [11], *viz*, $\widehat{\rho}_{\mathrm{GAR}} = \{MS_{\mathrm{B}} - \overline{y}(1-\overline{y})\}/\{(n-1)\tau(\Phi^{-1}(\overline{y})^2\}$. Here $MS_{\mathrm{B}}$ is the mean sum of squares between sires for the binary observations and $\overline{y}$ is the overall mean. The adjusted dependent variable and weights are: $\zeta_{\mathrm{GAR}} = \Phi^{-1}(\overline{y}) + (y-\overline{y})/\tau(\Phi^{-1}(\overline{y}))$ and $W_{\mathrm{GAR}} = \tau(\Phi^{-1}(\overline{y}))^2/\{\overline{y}(1-\overline{y}) - \rho\tau(\Phi^{-1}(\overline{y}))^2\}$. As long as the first-order approximation from [5] holds, and $q$ is not too small, $\widehat{\rho}_{\mathrm{GAR}}$ will be nearly unbiased. Actually, for this simple scheme, GAR may be shown to be equivalent to Williams' method of moments for estimating overdispersion (Williams, 1982). Starting from $\mathbf{u}_0 = 0$ and $\eta_0 = \Phi^{-1}(\overline{y})$, the adjusted dependent for IRREML is the same as for GAR, but the weights $w = \tau(\Phi^{-1}(\overline{y}))^2/\{\overline{y}(1-\overline{y})\}$ are smaller! Consequently, the first estimate $\widehat{\sigma}^2_S = \{MS_{\mathrm{B}} - \overline{y}(1-\overline{y})\}/\{n\tau(\Phi^{-1}(\overline{y}))^2\}$ underestimates $\sigma^2_S$ approximately by a factor $(n-1)/n$. Simulation results in Gilmour *et al* (1985) suggest that with further iteration underestimation by this factor persists. For extreme incidence, say close to 1, IRREML weights are approximately $\widehat{\eta}\,\tau(\widehat{\eta})$, as follows from Abramowitz and Stegun (1965, 26.2.12, p 932). Most of the information is in the negative-valued random effects, and over-shrinkage of random effects will yield smaller weights in the next iteration, *ie* 'residual variances' will be too high. Therefore, underestimation by IRREML may be expected to be more serious for extreme incidence, even when the first-order approximation from [5] still holds. Lack of information about individual random effects, because of small family size or extreme incidence, seems a serious problem with MAP/PQL/IRREML. The smaller weights in IRREML are a consequence of 'residual variances' being derived from predicted values of conditional variances. Alternative weights $w_0 = E(g'(\mu)^2 V(\mu))^{-1}$ for IRREML are suggested in Engel and Keen (1994). For the logit link evaluation of alternative weights is straightforward: $w_0 = \{2 + 2\exp(\sigma_1^2/2)\cosh(\mathbf{x}'\boldsymbol{\beta})\}^{-1}$, but for the probit link it is problematic. It is suggested that we use $w_0 = \{g'(\widehat{\mu})^2 E(V(\mu))\}^{-1}$ instead. Note that in the first step for the simple sire scheme this weight equals $w_{\mathrm{GAR}}$. Simulation results in Breslow and Clayton (1993) also show a negative bias for MAP/PQL/IRREML. However, Hoeschele and Gianola (1989) find a positive bias. Their simulation study concerns a sire model which includes 135 fixed HYS

effects. MAP/PQL/IRREML has smaller bias and smaller mean-squared error than GAR. For both methods an upward bias in the order of 20% (based on 45 simulations) of the true $h^2 = 0.25$ is observed. An upward bias is also apparent for some of the models simulated in Hoeschele *et al* (1987). Simulation results for overdispersed binomial data in Engel and Buist (1995) only indicate a serious upward bias for variance components estimated by IRREML when the true component value is small and the non-negativity constraints are active.

## Simulation results

Data are generated as described in Hoeschele and Gianola (1989) (referred to as HG). The 135 HYS effects are generated from a $N(0,\ \sigma^2_{\text{HYS}})$ distribution. For each HYS class, a sire has 0, 1 or 2 offspring with probabilities $1 - p_{\text{HYS}}$, $p_{\text{HYS}}/2$ and $p_{\text{HYS}}/2$ respectively. The HYS effects and design for sires and offspring are generated only once, after which the same HYS values and the same design are used in all subsequent simulations. HYS effects are included in the model as fixed effects. Other fixed effects are sire group effects: 4 groups with effects $-0.40$, $-0.15$ (the value $-0.10$ in HG was assumed to be a typing error), 0.15 and 0.40. The numbers of sires in the groups are 12, 14, 13 and 11. The 50 independent sire effects are generated from an $N(0,\ \sigma^2_{\text{S}})$ distribution, where $\sigma^2_{\text{S}} = h^2/(4 - h^2)$. The residuals for the liability are from an $N(0,\ 1)$ distribution. The overall constant on the probit scale is $-\Phi^{-1}(p_0)\ (1 + \sigma^2_{\text{HYS}} + \sigma^2_{\text{S}})^{0.5}$, where $p_0$ determines the overall incidence. Suppose that $\sigma^2_{\text{HYS}}$ corresponds to a proportion $f_{\text{HYS}}$ of $1 + \sigma^2_{\text{HYS}} + \sigma^2_{\text{S}}$, then $\sigma^2_{\text{HYS}} = (4f_{\text{HYS}}/(1 - f_{\text{HYS}}))/(4 - h^2)$. In HG, $h^2 = 0.25$, $f_{HYS} = 0.30$, $p_0 = 0.9$ and $p_{\text{HYS}} = 0.2$. The expected total number of records is 2 025, with about 40 offspring per sire. This is configuration 10, which is presented with some of the other configurations of parameter values studied in table IV.

For each configuration, either 1 or 2 series of 200 simulations are performed. In a series, HYS effects, sire-offspring configuration and data are all generated from a sequence of random numbers from the same seed. The first series corresponds to the same seed for all configurations. Therefore, for the first series, for example for configurations 3 and 8, the design is the same. Seeds of the second series are all different. In table IV bias (%bias) and root mean square error ($\%\sqrt{\text{MSE}}$) are both expressed as a percentage of the true value of $h^2$. In contrast with the results in Gilmour *et al* (1985) and in agreement with Hoeschele and Gianola (1989), with one exception, MAP/PQL/IRREML shows a positive bias. The exception is configuration 13 where HYS effects are not included, neither in the generation of the data nor in the model fitted. The negative value for this configuration indicates that, although the bias seems fairly independent of the size of the fixed effects, it may depend on the (relative) number of fixed effects in the model.

Table V shows that this is indeed so. Starting from the original HG scheme, using new seeds for generating the data, the number of fixed effects is reduced by factors 1/3, 1/2, 2/3 and 3/4. A reduction of 1/3, for instance, is effected by combination of HYS effects (2, 3), (5, 6), (8, 9) and so forth, replacing the original values for 2 levels by their mean value. The first series of 200 simulations refers to the same design used in all subsequent reductions. In the second series, a new design, which is reduced afterwards, is generated for 1, 1/3, ... . Bias goes from positive to negative.

**Table IV.** Simulation results for the HG sire scheme for IRREML and GAR. Bias and mean squared error for estimation of the heritability on the liability scale.

| *Configuration* | $h^2$ | $p_0$ | $p_{HYS}$ | $f_{HYS}$ | *%bias* | | | | $\%\sqrt{MSE}$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | *IRREML* | | *GAR* | | *IRREML* | *GAR* |
| 1 | 0.25 | 0.60 | 0.15 | 0.30 | 27.7 | (3.6) | 22.9 | (3.3) | 58.5 | 52.0 |
| 2 | 0.25 | 0.60 | 0.20 | 0.01 | 7.4 | (2.6) | 3.8 | (2.4) | 39.9 | 34.4 |
| | | | | | 18.0 | (2.6) | 13.0 | (2.3) | 40.4 | 35.1 |
| 3 | 0.25 | 0.60 | 0.20 | 0.02 | 7.8 | (2.6) | 4.1 | (2.4) | 37.7 | 34.2 |
| 4 | 0.25 | 0.60 | 0.20 | 0.15 | 9.1 | (2.7) | 5.1 | (2.5) | 39.6 | 35.6 |
| | | | | | 15.5 | (2.9) | 10.8 | (2.6) | 43.5 | 38.4 |
| 5 | 0.25 | 0.60 | 0.20 | 0.30 | 11.3 | (2.9) | 7.0 | (2.7) | 42.5 | 38.2 |
| | | | | | 16.9 | (2.6) | 11.8 | (2.4) | 41.2 | 36.0 |
| 6 | 0.25 | 0.60 | 0.30 | 0.001 | 3.6 | (2.1) | −0.6 | (1.9) | 29.4 | 26.8 |
| | | | | | 4.5 | (1.9) | 0.1 | (1.8) | 27.4 | 24.7 |
| 7 | 0.25 | 0.90 | 0.15 | 0.30 | 50.7 | (4.9) | 52.9 | (4.9) | 86.1 | 86.6 |
| 8 | 0.25 | 0.90 | 0.20 | 0.02 | 21.3 | (3.9) | 23.5 | (4.1) | 59.5 | 62.1 |
| 9 | 0.25 | 0.90 | 0.20 | 0.15 | 19.2 | (3.8) | 21.1 | (3.9) | 57.4 | 59.3 |
| | | | | | 24.2 | (3.7) | 24.3 | (3.7) | 58.2 | 58.0 |
| 10 | 0.25 | 0.90 | 0.20 | 0.30 | 19.2 | (4.2) | 20.6 | (4.2) | 62.5 | 62.6 |
| | | | | | 35.6 | (4.1) | 35.6 | (4.0) | 68.1 | 66.2 |
| 11 | 0.25 | 0.90 | 0.30 | 0.30 | 10.8 | (3.1) | 9.8 | (3.1) | 45.6 | 44.5 |
| 12 | 0.40 | 0.60 | 0.15 | 0.30 | 23.4 | (2.6) | 14.8 | (2.2) | 44.0 | 34.9 |
| 13 | 0.40 | 0.60 | 0.20 | – | −5.8 | (1.7) | −10.9 | (1.5) | 24.5 | 23.5 |
| 14 | 0.40 | 0.60 | 0.20 | 0.02 | 8.7 | (2.0) | 1.6 | (1.8) | 30.2 | 25.3 |
| | | | | | 13.0 | (2.1) | 4.4 | (1.8) | 32.9 | 26.2 |
| 15 | 0.40 | 0.60 | 0.20 | 0.15 | 9.1 | (2.0) | 1.6 | (1.8) | 30.1 | 24.9 |
| | | | | | 11.3 | (2.1) | 3.1 | (1.8) | 31.5 | 25.1 |
| 16 | 0.40 | 0.60 | 0.20 | 0.30 | 10.1 | (2.2) | 2.2 | (1.9) | 32.7 | 26.9 |
| | | | | | 15.0 | (2.2) | 6.2 | (1.9) | 34.8 | 27.4 |
| 17 | 0.40 | 0.60 | 0.30 | 0.02 | 3.4 | (1.8) | −3.9 | (1.5) | 25.0 | 21.9 |
| | | | | | 8.7 | (1.9) | 0.3 | (1.6) | 28.0 | 22.5 |
| 18 | 0.40 | 0.90 | 0.15 | 0.30 | 36.5 | (3.5) | 36.6 | (3.4) | 61.5 | 60.0 |
| 19 | 0.40 | 0.90 | 0.20 | 0.02 | 16.8 | (2.8) | 16.9 | (2.9) | 43.2 | 43.8 |
| 20 | 0.40 | 0.90 | 0.20 | 0.15 | 15.5 | (2.9) | 15.6 | (2.9) | 43.5 | 44.2 |
| | | | | | 21.8 | (3.0) | 20.7 | (3.0) | 47.6 | 47.1 |
| 21 | 0.40 | 0.90 | 0.20 | 0.30 | 14.5 | (3.0) | 13.9 | (3.0) | 45.1 | 44.0 |
| | | | | | 18.6 | (3.0) | 17.7 | (2.8) | 45.9 | 43.6 |
| 22 | 0.40 | 0.90 | 0.30 | 0.30 | 7.7 | (2.4) | 4.8 | (2.3) | 35.3 | 32.7 |

Standard errors in parentheses; $h^2$ = heritability; $p_0$ = incidence rate; $p_{HYS}$ = probability for a sire for progeny in a HYS class; $f_{HYS}$ = proportion of variance explained by the HYS effects.

The negative bias agrees with the calculations in the preceding section for the simple sire model and with the results in Gilmour *et al* (1985), where an overall constant was the only fixed effect in the model. Data for configurations 10 and 16 was also generated with random HYS effects, with a new set of HYS effects for each simulation, and analysed with HYS as a random factor in the model. Estimated bias was −35.8 (2.7)% for configuration 10 and −11.8 (1.7)% for configuration 16. Corresponding root mean square errors were 52.0 and 27.3%, respectively. Bias and root mean square error are reduced when the progeny size is increased, see, for example, configurations 18, 21 and 22. Estimators are also less biased when incidence is less extreme, *eg*, configurations 3 *versus* 8 and 1 *versus* 7. Differences between series within configurations are sometimes greater than would be expected on the basis of the standard errors involved, showing that the configuration of sires and offspring is also of importance.

**Table V.** Simulation results for IRREML, GAR and IRREML ($w_0$) for the HG scheme, with smaller numbers of HYS effects.

| *Reduction in HYS effects* | *%bias* | | | *%√MSE* | | |
|---|---|---|---|---|---|---|
| | *IRREML* | *GAR* | *IRREML* ($w_0$) | *IRREML* | *GAR* | *IRREML* ($w_0$) |
| Original scheme | 21.7 (4.1)<br>18.7 (3.8) | 21.2 (4.0)<br>19.8 (3.8) | 11.6 (3.8) | 62.4<br>58.1 | 60.3<br>57.7 | 54.6 |
| 1/3 | 0.5 (3.6)<br>3.8 (3.5) | 3.5 (3.7)<br>6.3 (3.6) | −9.0 (3.1) | 51.5<br>49.6 | 52.0<br>51.2 | 45.4 |
| 1/2 | −5.3 (3.1)<br>−1.9 (3.2) | −3.8 (3.1)<br>1.1 (3.2) | −13.8 (2.7) | 43.8<br>44.9 | 44.0<br>45.8 | 40.4 |
| 2/3 | −8.9 (3.2)<br>−8.1 (2.9) | −7.7 (3.4)<br>−5.8 (3.0) | −18.1 (2.9) | 46.5<br>41.6 | 48.2<br>42.7 | 44.2 |
| 3/4 | −14.9 (6.0)<br>−9.4 (3.1) | −13.2 (6.1)<br>−5.3 (3.3) | −20.9 (3.0) | 46.0<br>45.3 | 46.8<br>47.2 | 47.7 |
| No HYS and sire group effects | −13.1 (3.1) | −2.7 (3.6) | −14.3 (2.8) | 45.4 | 51.1 | 41.8 |

Bias and root mean square error for estimated heritability are expressed as a percentage of the true value of $h^2$. Standard errors in parentheses.

GAR was programmed, similar to MAP/PQL/IRREML, in terms of Fisher scoring for the updates of the sire variance. Estimates are the same as for the original method proposed, which uses EM steps, but speed of convergence is often increased by at least a factor 10. Some results, using the same seeds as for MAP/PQL/IRREML, are presented in tables IV and V. For high incidence ($p_0 = 0.9$) results of MAP/PQL/IRREML and GAR are comparable. For moderate incidence ($p_0 = 0.6$), the bias for GAR is clearly less than for MAP/PQL/IRREML. GAR also has smaller mean square error than MAP/PQL/IRREML at the lower incidence, although the difference is less marked. In all cases, the root

mean square error is considerably larger than the corresponding bias. Plots of the estimated $h^2$ values of MAP/PQL/IRREML against GAR suggest a strong, fairly linear relationship. Correlations between sire predictions from MAP/PQL/IRREML and GAR are high, *eg*, over 0.99 for the first series of configurations 10 and 16.

Table V also includes results obtained for IRREML with the alternative weights $w_0 = \tau(\eta)^2/\{p(1-p) - \rho\tau(\lambda_p\eta)^2\}$ from the previous section. There is a distinct change in the bias due to the change of weights. However, although bias is considerably improved for the top lines in the table, underestimation for the bottom lines has become more serious.

In table VI, approximate standard errors of heritability estimates from MAP/PQL/IRREML are compared with standard errors estimated from the series of 200 simulations (referred to as empirical values). The approximate standard errors, based on Fisher information assuming normality for the adjusted dependent variate, perform quite well, as was also observed in Engel and Buist (1995). These standard errors are standard output in Genstat 5.

**Table VI.** Empirical standard errors for $h^2$ from the simulation compared with approximate standard errors.

| *Configuration* | *Empirical standard error* | *Approximate standard error* | |
|---|---|---|---|
| | | *Mean* | *Percentage points* |
| 4 | 0.096 | 94.4 | [75.8; 115.7] |
| | 0.101 | 92.1 | [71.3; 113.4] |
| 5 | 0.102 | 92.7 | [72.5; 113.4] |
| | 0.094 | 103.3 | [80.5; 125.0] |
| 6 | 0.073 | 100.3 | [78.7; 122.2] |
| | 0.068 | 106.5 | [86.5; 128.6] |
| 9 | 0.135 | 98.7 | [78.7; 119.5] |
| | 0.132 | 98.3 | [78.2; 119.0] |
| 10 | 0.149 | 94.4 | [75.0; 115.2] |
| | 0.145 | 99.5 | [81.2; 118.7] |
| 15 | 0.115 | 101.3 | [82.7; 119.8] |
| | 0.118 | 98.6 | [80.4; 118.8] |
| 16 | 0.124 | 96.4 | [77.8; 114.5] |
| | 0.126 | 96.7 | [78.0; 114.0] |
| 20 | 0.163 | 97.2 | [77.9; 114.9] |
| | 0.169 | 96.6 | [78.7; 114.0] |
| 21 | 0.171 | 95.8 | [79.9; 112.4] |
| | 0.168 | 99.8 | [81.3; 115.6] |

Mean, 10 and 90% percentage points of the approximate standard errors are presented as percentages of the empirical value.

The approximately linear relationship between IRREML and GAR estimates within a configuration of parameter values, and the similar standard errors, suggest that it should be possible to correct for bias in IRREML, at the least in those cases where GAR performs well. For incidence 0.90 and the full set of 135 HYS effects, IRREML and GAR have large positive bias of similar size. In this case the direction of the bias is in line with results for GLMs, where bias correction often involves

shrinkage towards the origin. Possibly, the results of Cordeiro and McCullagh (1991), involving an extra iteration step for adjusted response variables, may be extended to minimization of the penalized deviance, thus improving estimates $\widehat{\beta}$ and predictions $\widehat{u}$. This would imply modification of the adjusted dependent variate $\zeta$.

Users of MAP/PQL/IRREML should be aware of the problems involved when family sizes are small, or in the context of an animal model, when many animals are only weakly related. With extreme incidence, say over 0.90, and a sizeable number of HYS effects, say in the order of 6% of the number of binary observations, MAP, PQL, IRREML and GAR are liable to seriously overestimate heritability, and actual selection response may be considerably less than expected on the basis of model calculations.

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# Chapter 7

## Analysis of a mixed model for ordinal data by iterative re-weighted REML

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IRREML is extended towards threshold models for ordinal data. Estimation of additional shape parameters, i.e. parameters modelling variance heterogeneity on the underlying scale, is included as well.

# Analysis of a mixed model for ordinal data by iterative re-weighted REML

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**Summary** An estimation procedure will be presented for a class of threshold models for ordinal data. These models may include both fixed and random effects with associated components of variance on an underlying scale. The residual error distribution on the underlying scale may be rendered greater flexibility by introducing additional shape parameters, e.g. a kurtosis parameter or parameters to model heterogeneous residual variances as a function of factors and covariates. The estimation procedure is an extension of an iterative re-weighted restricted maximum likelihood procedure, originally developed for generalized linear mixed models. This procedure will be illustrated with a practical problem involving damage to potato tubers and with data from animal breeding and medical research from the literature.

**Keywords**: threshold model, variance components, variance heterogeneity

## 1. Introduction

A flexible class of mixed models for ordered categorical data will be presented. Categories correspond to intervals defined by cutpoints on an underlying scale. A category is observed when an underlying variable is in the corresponding interval. Fixed and random effects with associated variance components are introduced for the underlying random variable. Parameters are estimated by extending the iterative method proposed for generalized linear mixed models (GLMMs) by Engel and Keen (1994). In each iteration step an adjusted dependent variate and weights are calculated and parameter estimates are updated applying weighted restricted maximum likelihood (REML, see Patterson and Thompson, 1971) to an approximate linear mixed model for the adjusted dependent variate. This procedure will be referred to as iterative re-weighted REML (IRREML). Estimation is analogous to iterative re-weighted least squares for ordinary generalized linear models (e.g. McCullagh and Nelder, 1989, § 2.5), but with REML methodology replacing weighted least squares. Details may be found in Engel and Keen (1994). For GLMMs, IRREML is equivalent to estimation procedures presented by Schall (1991) and Breslow and Clayton (1993) (penalized quasi-likelihood). Standard software for REML, with facilities for introducing weights and restricting the residual variance to a fixed value, can be employed. For the examples in this paper we used the statistical programming language Genstat 5 (1993).

The distribution for the residuals on the underlying scale determines a link function for the cumulative probabilities of not exceeding a fixed category. Cutpoints are regarded as parameters in this link function and estimated by adopting a linearizing strategy due to

Pregibon (1980). This amounts to Taylor expansion of cumulative probabilities, or equivalently individual category probabilities, both with respect to the fixed and random effects and to the unknown cutpoints, ignoring second and higher order terms. In each iteration, the approximate linear mixed model for the adjusted dependent variate is extended with extra covariates, derived from the expansion, for estimation of the cutpoints. The same approach works for additional shape parameters of the underlying residual distribution as well. Examples will be given where the underlying residual distribution is from a family of Student distributions with unknown number of degrees of freedom as a kurtosis parameter, or where the underlying distribution is normal, with a factorial model for the logarithm of the heterogeneous residual variances. In addition to the traditional choice of an underlying standard normal or standard logistic distribution for the residuals, this offers useful tools for checking and improving goodness of fit of the threshold model.

Without additional random effects and components of variance in the model, IRREML is equivalent with maximum likelihood (ML) estimation. With additional random effects, this equivalence no longer holds, although estimation by IRREML can be regarded as an approximation to ML estimation, with a REML type adjustment for the components of variance. However, in contrast to ML estimation, which is quickly bogged down by the need for numerical integration, numerical restrictions for IRREML are the same as for conventional mixed models for normal data. Restrictions pertain to the size of matrices to be inverted. This can be dealt with to a large extent by eliminating (absorbing) factors with a large number of levels, see e.g. Engel (1990) for details, and the example in Section 5 for an illustration.

In the next section the estimation procedure will be introduced for the threshold model with fixed effects only and normal residuals on the underlying scale. In section 3 additional random effects and components of variance will be introduced. In Section 6 the model is extended with extra shape parameters for the residual distribution. In Sections 4, 5, 7, 8 and 9 examples are presented. The connection with ML estimation and other estimation procedures from the literature is the subject of Section 10.

## 2 A threshold model with fixed effects only

Consider the linear model:

$$\mathbf{z} = \boldsymbol{\eta} + \boldsymbol{\epsilon} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon},$$

where $\mathbf{X}$ is a design matrix, $\boldsymbol{\beta}$ is a vector of unknown effects, e.g. treatment effects, and $\boldsymbol{\epsilon}$ is a vector of independent normal residuals with mean 0 and variance $v^2$. Suppose that z is not observed, but its class $j = 1 \ldots J$ with respect to cutpoints $-\infty = \theta_0 < \theta_1 < \ldots < \theta_J = \infty$, i.e. $y = j$ is observed when $\theta_{j-1} < z \leq \theta_j$. We will refer to z as the underlying variable. Variable y is the ordered categorical variable which is actually observed.

When several individuals or units correspond to e.g. the same treatment, they may be grouped together. For the i-th group, let $n_{ij}$ be the number of observations in class j and $\mathbf{n}_i = (n_{i1} \ldots n_{iJ})'$ be the vector of counts. $\mathbf{n}_i$ follows a multinomial distribution with total $N_i = n_{i1} + \ldots + n_{iJ}$ and probabilities:

$$\pi_{ij} = \Phi(\theta^*_{ij}) - \Phi(\theta^*_{ij-1}), \quad j = 1 \ldots J, \tag{1}$$

where $\Phi(.)$ is the cdf of the standard normal distribution and $\theta^*_{ij} = (\theta_j - \eta_i) / \nu$. For ungrouped data $n_{ij} = 0$ or 1 and $N_i = 1$ for all i. Both for grouped and ungrouped data, we will refer to i = 1, 2, ... as the units.

When the cutpoints are unknown, without loss of generality, $\nu^2$ may be fixed at any convenient positive value, typically 1 in this case. Also, when there is an overall mean in $\boldsymbol{\beta}$, one of the cutpoints or the overall mean may be fixed at an arbitrary value. Here, unless stated otherwise, $\theta_1 = 0$. The cutpoints are collected in a vector $\boldsymbol{\xi}$. We will first derive estimating equations for $\boldsymbol{\beta}$ for known $\boldsymbol{\xi}$. Then, for unknown $\boldsymbol{\xi}$, additional estimating equations will be derived for the cutpoints.

### 2.1 Estimation for known $\boldsymbol{\xi}$

In deriving estimating equations we will closely follow the iterative re-weighted least squares algorithm for generalized linear models (GLMs) (see e.g. McCullagh and Nelder, 1989, §2.5). The linear combination $\boldsymbol{\eta} = \mathbf{X}\boldsymbol{\beta}$ will be referred to as the linear predictor. For the i-th unit: $\mu_{ij} = N_i\pi_{ij} = h_{ij}(\eta_i) = h_{ij}(\mathbf{x}_i'\boldsymbol{\beta})$, where $\mu_{ij}$ is the mean of count $n_{ij}$ and function $h_{ij}(.)$ follows from (1). In GLM terminology, functions $h_{ij}(.)$ define an inverse (composite) link function.

Suppose that $\mu_{ij}$, $\eta_i$, ... are evaluated for starting values $\boldsymbol{\beta}_0$ for $\boldsymbol{\beta}$. Parameter $\nu$ will be fixed throughout at value 1. An adjusted dependent variate $\zeta$ is defined by:

$$\zeta_{ij} = \eta_{0\,i} + (n_{ij} - \mu_{0\,ij}) / h'_{ij}(\eta_{0\,i};\, \boldsymbol{\xi}), \tag{2}$$

where $h'_{ij}(\eta;\, \boldsymbol{\xi})$ is the derivative with respect to $\eta$. For later use, functional dependence on $\boldsymbol{\xi}$ is included in the notation. It is readily shown, see e.g. Engel and Keen (1994), that vector $\boldsymbol{\zeta} = (\zeta_{11} \ldots \zeta_{1J}, \zeta_{21} \ldots \zeta_{2J}, \ldots)'$ has approximate moments:

$$E(\boldsymbol{\zeta}) = \tilde{\mathbf{X}}\boldsymbol{\beta} \quad \text{and} \quad \mathrm{Var}(\boldsymbol{\zeta}) = \mathbf{R}, \tag{3}$$

where $\tilde{\mathbf{X}} = \mathbf{X} \otimes \mathbf{1}_J$, $\otimes$ is the Kronecker product and $\mathbf{1}_J$ is a vector of length J with all elements equal to 1. $\mathbf{R}$ is a block diagonal matrix with blocks $\mathbf{R}_i = \mathbf{B}_i\boldsymbol{\Sigma}_i\mathbf{B}_i$ along the diagonal. $\boldsymbol{\Sigma}_i$ is the covariance matrix of the multinomial distribution for the i-th unit: $\Sigma_i = N_i\{\mathrm{diag}(\pi_{0\,i}) - \boldsymbol{\pi}_{0\,i}\boldsymbol{\pi}_{0\,i}'\}$, where $\boldsymbol{\pi}_i = (\pi_{i1} \ldots \pi_{iJ})'$ is the vector of probabilities for that unit. $\mathbf{B}_i$ is a diagonal matrix with elements $h'_{ij}(\eta_{0\,i};\, \boldsymbol{\xi})^{-1}$ along the diagonal. $\boldsymbol{\Sigma}_i$ is not a full rank

matrix. Generalized inverses of $\mathbf{\Sigma}_i$ are of the form: $\mathbf{\Sigma}_i^- = \text{diag}(\mu_{0\,ij}^{-1}) - \tau \mathbf{1}_j \mathbf{1}_j'$ with $\tau$ an arbitrary constant, see McCullagh and Nelder (1989, §5.3.3). Parameters $\boldsymbol{\beta}$ are updated by weighted regression on $\zeta$. After each iteration, $\zeta$ and $\mathbf{R}$ are updated for the current estimates for $\boldsymbol{\beta}$ solved from the *normal equations*:

$$\tilde{\mathbf{X}}\mathbf{R}^-\tilde{\mathbf{X}}\boldsymbol{\beta} = \tilde{\mathbf{X}}'\mathbf{R}^-\zeta. \tag{4}$$

Because the $\mu_{ij}$ within a unit sum to the fixed total $N_i$, equations (4) are independent of the generalized inverse used. Choosing $\tau = 0$, it follows that the equations can be set up as if the observations $n_{i1}$ ... $n_{ij}$ are independent Poisson counts with means $\mu_{i1}$ ... $\mu_{ij}$. In that case $\mathbf{R}^-$ will be a diagonal matrix of iterative weights

$$w_{ij} = h_{ij}'(\eta_i;\ \xi)^2 / \mu_{ij}, \tag{5}$$

similar to an ordinary GLM. The (composite) link function as an inverse of functions $h_{ij}(.)$ exists only locally in the neighbourhood of points $\eta$ with $h_{ij}'(\eta;\ \xi) \neq 0$. Points where $h_{ij}'(\eta;\ \xi) = 0$ are obviously problematic. When, similar to the approach in Thompson and Baker (1981), the adjusted dependent variate is modified by multiplication with $h_{ij}'(\eta;\ \xi)$, the regressors, when modified in the same way, become equal to 0. This suggests that offending observations may be ignored in an iteration step. For known cutpoints, the iteration process can be condensed by employing a "pooled" adjusted dependent variate $\zeta_i$ and "pooled" weights $w_i$:

$$\zeta_i = \sum_j w_{ij}\zeta_{ij} / \sum_j w_{ij} = \eta_i + \sum_j \{h_{ij}'(\eta_i;\ \xi)(n_{ij}-\mu_{ij})/v_{ij}\} / w_i \text{ and } w_i = \sum_j w_{ij} = \sum_j h_{ij}'(\eta_i;\ \xi)^2 / \mu_{ij}.$$

Pooling reduces the number of "observations" $\zeta$ and effectively removes problems with 0 derivatives. When cutpoints are unknown, which will be discussed in the next section, pooling is not possible. Note that the model with known cutpoints has some use in practice, for instance when a variable is observed upto the nearest integer.

### 2.2 Estimation for unknown $\xi$

We now have to supply additional estimating equations for the cutpoints in $\xi$. In GLM terminology, $\xi$ can be regarded as a vector of parameters in the (inverse) link function. An approach similar to Pregibon (1980) (see also McCullagh and Nelder, 1989, §11.3) will be used. The means $\mu_{ij}$ are linearized with respect to both $\eta_i$ and $\xi$ around current values $\eta_{0i}$ and $\xi_0$:

$$\mu_{ij} \approx \mu_{0ij} + [\partial h_{ij}(\eta_i;\ \xi)/\partial \eta_i]_{\eta 0i, \xi 0} (\eta_i - \eta_{0i}) + [\partial h_{ij}(\eta_i;\ \xi)/\partial \xi]'_{\eta 0i, \xi 0} (\xi - \xi_0),$$

which implies that:

$$\eta_{0i} + (\mu_{ij}-\mu_{0ij}) / h'_{ij}(\eta_{0i}, \xi_0) \approx \eta_i + \{[\partial h_{ij}(\eta_i; \xi)/\partial\xi]'_{\eta oi,\xi o} / [\partial h_{ij}(\eta_i; \xi)/\partial\eta_i]_{\eta oi,\xi o}\}(\xi-\xi_0),$$

and consequently:

$$E(\zeta_{ij}) \approx \eta_i + \{[\partial h_{ij}(\eta_i; \xi)/\partial\xi]'_{\eta oi,\xi o} / [\partial h_{ij}(\eta_i; \xi)/\partial\eta_i]_{\eta oi,\xi o}\}\ \Delta\xi,$$

where $\Delta\xi = \xi - \xi_0$. This suggests to extend the set of explanatory variables in the weighted regression for $\zeta$ with columns of the matrix $\mathbf{X}_\xi$ with elements $[\partial h_{ij}(\eta_i; \xi)/\partial\xi_k] / [\partial h_{ij}(\eta_i; \xi)/\partial\eta_i]$, evaluated for current values $\eta_0$ and $\xi_0$, and with coefficient vector $\Delta\xi$. $\xi$ can be updated by: $\xi = \xi_0+\Delta\xi$. This can be combined with the iterations in Section 2.1, updating $\mathbf{X}_\xi$ as a part of $\tilde{\mathbf{X}}$ after each iteration. The necessary derivatives are:

$$\partial h_{ij}(\eta_i; \xi)/\partial\xi_k = N_i\{(\partial\Phi(\theta^*_{ij})/\partial\xi_k) - (\partial\Phi(\theta^*_{i\,j-1})/\partial\xi_k)\} =$$

$$N_i\phi(\theta^*_{ij}) \text{ when } \xi_k = \theta_j,\ -N_i\phi(\theta^*_{i\,j-1}) \text{ when } \xi_k = \theta_{j-1}, \text{ and 0 otherwise,}$$

and (6)

$$\partial h_{ij}(\eta_i; \xi)/\partial\eta_i = N_i\{\phi(\theta^*_{i\,j-1}) - \phi(\theta^*_{ij})\},$$

where $\phi(.)$ is the pdf of the standard normal distribution.

Some algebra shows that the combined iterative proces is equivalent to Fisher scoring for maximising the product multinomial likelihood of counts $n_{ij}$. Thus, the final estimates $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{\xi}}$ are ML estimates. The equivalence with ML estimation no longer holds in the next section, where the estimation procedure is extended for additional random effects in the linear predictor $\boldsymbol{\eta}$.

## 3 A threshold model with additional random effects

Now, suppose that the underlying variable follows a linear mixed model:

$$\mathbf{z} = \boldsymbol{\eta} + \boldsymbol{\epsilon} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \boldsymbol{\epsilon}, \tag{7}$$

where $\mathbf{Z}$ is a design matrix for additional random effects collected in vector $\mathbf{u}$; $\mathbf{u} \sim N(\mathbf{0}, \mathbf{G})$. Often $\mathbf{G}$ is a blockdiagonal matrix with blocks $\sigma^2_1\mathbf{A}_1$ ... $\sigma^2_c\mathbf{A}_c$ along the diagonal, where $\mathbf{A}_1$ ... $\mathbf{A}_c$ are known matrices and $\sigma^2_1$ ... $\sigma^2_c$ are unknown components of variance to be estimated from the data. Here, we will assume that $\mathbf{A}_1$ ... $\mathbf{A}_c$ are identity matrices. Again, we start under the assumption that cutpoints in $\xi$ are known. Moments in (3) still hold, but conditional upon $\mathbf{u}$. The first two marginal moments of the adjusted dependent $\zeta$ variate from (2) are approximately:

$$E(\zeta) = \tilde{\mathbf{X}}\boldsymbol{\beta} \text{ and } \mathrm{Var}(\zeta) = \tilde{\mathbf{Z}}\mathbf{G}\tilde{\mathbf{Z}}' + \mathbf{R},$$

where $\tilde{\mathbf{X}}$ and $\mathbf{R}$ are defined as before and $\tilde{\mathbf{Z}} = \mathbf{Z} \otimes \mathbf{1}_J$. Parameters will be estimated by iterative use of REML, as described in Engel and Keen (1994), i.e. iterative weighted regression from Section 2 will be replaced by iterative weighted REML. After each iteration step, $\zeta$ and $\mathbf{R}$ are updated employing current estimates for $\beta$ and predictions for $\mathbf{u}$ solved from the *mixed model equations* (see e.g. Engel, 1990):

$$\begin{pmatrix} \tilde{\mathbf{X}}'\mathbf{R}^- \tilde{\mathbf{X}} & \tilde{\mathbf{X}}'\mathbf{R}^- \tilde{\mathbf{Z}} \\ \tilde{\mathbf{Z}}'\mathbf{R}^- \tilde{\mathbf{X}} & \tilde{\mathbf{Z}}'\mathbf{R}^- \tilde{\mathbf{Z}} + \mathbf{G}^{-1} \end{pmatrix} \begin{pmatrix} \beta \\ \mathbf{u} \end{pmatrix} = \begin{pmatrix} \tilde{\mathbf{X}}'\mathbf{R}^- \zeta \\ \tilde{\mathbf{Z}}'\mathbf{R}^- \zeta \end{pmatrix} . \tag{8}$$

The mixed model equations (8) replace the normal equations (4). They are independent of the generalized inverse $\mathbf{R}^-$ used. Again, we will choose the diagonal generalized inverse with elements $w_{ij}$ from (5). Components of variance will be updated by one or several steps of the Fisher scoring algorithm for REML, applied to the approximate linear mixed model for $\zeta$ with residual weights $w_{ij}$. Since one step of Fisher scoring, or equivalently one step of Rao's MINQUE (Rao, 1973, §4j.), can be formulated in terms of the solution and bits and pieces of the mixed model equations (see e.g. Engel, 1990), estimates for components of variance are independent of the choice of generalized inverse. In particular it follows that estimates are the same for multinomial or independent Poisson counts. For unknown cutpoints, again Pregibon's method is used to supply the additional estimating equations.

With additional random effects in the model, the estimation procedure is no longer equivalent to ML estimation. However, for given values of the components of variance, estimation of $\beta$ and prediction of u is equivalent to maximization of the joint pdf of observations and random effects. This implies that the final estimates $\hat{\beta}$ and predictions $\hat{\mathbf{u}}$ minimize a penalized deviance $D + \mathbf{u}'\mathbf{G}^{-1}\mathbf{u}$, where D is the deviance of the observations conditional upon the random effects. A similar property holds for IRREML applied to GLMMs, see e.g. Engel, Buist and Visscher (1995). An approximate relationship with ML estimation will be discussed in Section 10. We will now look at two examples, before we extend the threshold model with extra shape parameters.

## 4 Footshape in lambs

The data is reproduced in Gilmour, Anderson and Rae (1987). 2513 lambs are scored in three ordered categories based on the presence of deformities in the feet. Fixed effects correspond to 2 years and 5 strains nested within years. Random effects correspond to 34 sires nested within strains. Sires are assumed to be unrelated. Of interest is the heritability, which is defined as four times the intraclass correlation $\rho = \sigma_1^2 / (\sigma_1^2+1)$ for underlying normal random effects and residuals with $v^2 = 1$.

Results obtained with IRREML and with the marginal approach of Gilmour, Anderson and Rae (1987) are shown in Table 1. Results of the two methods are seen to be very similar.

**Table 1.** Estimates and standard errors for the footshape data. For coding of fixed effects contrasts B1, B2 and B3 see Gilmour, Anderson and Rae (1987)

| | IRREML | Gilmour et al. |
|---|---|---|
| Intraclass correlation $\rho$ | 0.056 (0.020) | 0.060 (0.019)[†] |
| Thresholds[††] | 0.374 (0.050) | 0.370 (0.052) |
| | 1.641 (0.061) | 1.603 (0.061) |
| Effects: | | |
| Year | −0.142 (0.052) | −0.139 (0.052) |
| B1 | −0.377 (0.077) | −0.370 (0.076) |
| B2 | −0.316[†] (0.104) | −0.304 (0.103) |
| B3 | 0.099 (0.070) | 0.098 (0.070) |

[†] The standard error is a correction of the value 0.144 in Gilmour, Anderson and Rae (1987) (Gilmour, personal communication).

[††] In Genstat procedure CLASS the first threshold is normally fixed at value 0, but for ease of comparison with the results from Gilmour et al. separate values are calculated fixing the overall mean at value 0.

## 5 Damage to potato tubers

Data result from one of a series of experiments to reduce damage to potato tubers due to a potato lifter. Experiments were performed at the Institute of Agricultural Engineering (IMAG-DLO) in Wageningen, The Netherlands. One source of damage is the type of rod used in the lifter. In the experiment under consideration eight types of rod were compared. It is an emperical fact that degree of damage varies considerably between potato varieties and years. To mimic this variety, two energy levels, six varieties and three weight classes were included in the experiment. Observations were obtained for the combinations of rods, energy levels, varieties and weight classes. Most combinations involved about 20 potato tubers. For some combinations there are no data due to an insufficient number of large potatoes. Two combinations are interchanged, resulting in 40 tubers for the one combination and none for the other. Tubers were dropped from a height determined by the energy level required. To determine the damage, each tuber was peeled and the degree of blue colouring was classified into one of four classes (class 1 for no damage to class 4 for severe damage). Observations in the form of counts per class and combination are reproduced in Table 2.

Of interest are overall differences between rods. Other factors are introduced to create sufficient variety in experimental conditions and are not of primary interest themselves. There is certainly no interest in a detailed description of interaction effects. A pragmatic approach was followed where main effects were introduced as fixed effects and interactions as random effects. This offers a simple summary in terms of main effects, as well as a quick screening device to judge importance of interactions by the size of their

**Table 2.** The potato damage data. Counts n for the four classes from "no damage" to "severe damage"

| | | Energy .5 (Joule) | | | | | | | | | | | | Energy 1 (Joule) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Weight class | | 1 | | | | 2 | | | | 3 | | | | 1 | | | | 2 | | | | 3 | | | |
| Var | Rod | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 | 1 | 5 | 14 | 1 | 0 | 5 | 31 | 2 | 1 | 0 | 0 | 0 | 0 | 2 | 5 | 7 | 6 | 2 | 12 | 6 | 0 | 10 | 7 | 3 | 0 |
| | 2 | 8 | 11 | 1 | 0 | 6 | 11 | 1 | 0 | 7 | 10 | 2 | 0 | 8 | 11 | 1 | 0 | 5 | 12 | 3 | 0 | 4 | 15 | 1 | 0 |
| | 3 | 6 | 13 | 0 | 0 | 5 | 13 | 0 | 0 | 1 | 19 | 0 | 0 | 3 | 7 | 4 | 4 | 2 | 10 | 5 | 3 | 3 | 11 | 4 | 2 |
| | 4 | 2 | 9 | 6 | 3 | 2 | 11 | 6 | 0 | 4 | 13 | 3 | 0 | 0 | 0 | 1 | 18 | 0 | 2 | 5 | 13 | 0 | 2 | 14 | 4 |
| | 5 | 11 | 8 | 0 | 0 | 16 | 4 | 0 | 0 | 15 | 4 | 0 | 1 | 9 | 6 | 3 | 0 | 9 | 9 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 6 | 12 | 5 | 2 | 0 | 15 | 5 | 0 | 0 | 11 | 4 | 0 | 5 | 5 | 12 | 1 | 0 | 12 | 6 | 1 | 1 | 7 | 10 | 3 | 0 |
| | 7 | 8 | 12 | 0 | 0 | 9 | 7 | 3 | 1 | 11 | 9 | 0 | 0 | 9 | 9 | 1 | 1 | 5 | 12 | 0 | 0 | 4 | 4 | 1 | 0 |
| | 8 | 15 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 17 | 2 | 1 | 0 | 19 | 0 | 0 | 0 | 17 | 1 | 0 | 0 | 19 | 1 | 0 | 0 |
| 2 | 1 | 4 | 5 | 4 | 7 | 5 | 7 | 5 | 1 | 9 | 7 | 2 | 0 | 0 | 5 | 6 | 7 | 1 | 4 | 6 | 9 | 1 | 7 | 6 | 6 |
| | 2 | 8 | 3 | 0 | 0 | 13 | 6 | 1 | 0 | 18 | 2 | 0 | 0 | 6 | 9 | 2 | 3 | 5 | 11 | 2 | 1 | 7 | 12 | 1 | 0 |
| | 3 | 3 | 10 | 6 | 1 | 5 | 12 | 3 | 0 | 13 | 6 | 0 | 0 | 1 | 6 | 5 | 7 | 3 | 6 | 6 | 5 | 7 | 6 | 6 | 1 |
| | 4 | 1 | 3 | 11 | 5 | 0 | 8 | 11 | 1 | 0 | 9 | 9 | 2 | 0 | 3 | 3 | 14 | 0 | 1 | 7 | 12 | 2 | 7 | 10 | 1 |
| | 5 | 16 | 3 | 1 | 0 | 10 | 9 | 1 | 0 | 16 | 2 | 1 | 0 | 6 | 12 | 2 | 0 | 7 | 9 | 4 | 0 | 8 | 11 | 1 | 0 |
| | 6 | 16 | 3 | 0 | 0 | 10 | 7 | 1 | 1 | 15 | 3 | 2 | 0 | 16 | 3 | 1 | 0 | 11 | 6 | 3 | 0 | 14 | 6 | 0 | 0 |
| | 7 | 11 | 9 | 0 | 0 | 11 | 6 | 1 | 0 | 14 | 5 | 1 | 0 | 11 | 6 | 0 | 0 | 15 | 2 | 3 | 0 | 16 | 3 | 0 | 0 |
| | 8 | 10 | 10 | 0 | 0 | 13 | 6 | 0 | 0 | 12 | 3 | 2 | 1 | 11 | 6 | 2 | 1 | 13 | 6 | 0 | 0 | 13 | 7 | 0 | 0 |
| 3 | 1 | 3 | 2 | 8 | 7 | 6 | 8 | 5 | 1 | 3 | 15 | 2 | 0 | 1 | 2 | 2 | 15 | 0 | 0 | 4 | 16 | 2 | 3 | 9 | 6 |
| | 2 | 18 | 1 | 0 | 0 | 12 | 6 | 1 | 1 | 10 | 6 | 2 | 2 | 10 | 5 | 2 | 2 | 9 | 2 | 8 | 1 | 10 | 6 | 4 | 0 |
| | 3 | 5 | 7 | 4 | 4 | 10 | 8 | 0 | 2 | 8 | 9 | 2 | 1 | 2 | 2 | 3 | 12 | 2 | 5 | 5 | 8 | 3 | 5 | 9 | 2 |
| | 4 | 1 | 4 | 6 | 9 | 2 | 6 | 10 | 2 | 3 | 5 | 10 | 1 | 1 | 0 | 5 | 13 | 0 | 0 | 2 | 18 | 1 | 0 | 7 | 12 |
| | 5 | 12 | 7 | 1 | 0 | 16 | 4 | 0 | 0 | 16 | 3 | 0 | 1 | 14 | 5 | 0 | 1 | 13 | 5 | 1 | 0 | 13 | 7 | 0 | 0 |
| | 6 | 16 | 3 | 0 | 1 | 14 | 5 | 0 | 0 | 15 | 5 | 0 | 0 | 11 | 6 | 1 | 1 | 15 | 4 | 0 | 1 | 13 | 5 | 0 | 0 |
| | 7 | 20 | 0 | 0 | 0 | 16 | 3 | 0 | 0 | 15 | 5 | 0 | 0 | 14 | 5 | 0 | 1 | 16 | 3 | 0 | 0 | 12 | 8 | 0 | 0 |
| | 8 | 18 | 2 | 0 | 0 | 16 | 3 | 0 | 1 | 16 | 4 | 0 | 0 | 12 | 4 | 0 | 1 | 18 | 2 | 0 | 0 | 14 | 6 | 0 | 0 |
| 4 | 1 | 4 | 9 | 7 | 0 | 4 | 11 | 3 | 1 | 10 | 9 | 1 | 0 | 0 | 1 | 6 | 13 | 0 | 3 | 5 | 12 | 3 | 7 | 8 | 2 |
| | 2 | 12 | 8 | 0 | 0 | 17 | 2 | 0 | 1 | 16 | 3 | 1 | 0 | 8 | 6 | 2 | 2 | 10 | 9 | 0 | 0 | 12 | 6 | 0 | 1 |
| | 3 | 10 | 10 | 0 | 0 | 10 | 9 | 0 | 0 | 15 | 4 | 0 | 0 | 2 | 2 | 6 | 7 | 9 | 11 | 0 | 0 | 7 | 5 | 5 | 2 |
| | 4 | 2 | 8 | 4 | 6 | 4 | 8 | 6 | 1 | 5 | 11 | 4 | 0 | 1 | 0 | 3 | 15 | 0 | 5 | 9 | 6 | 0 | 1 | 10 | 8 |
| | 5 | 17 | 2 | 0 | 0 | 18 | 2 | 0 | 0 | 17 | 2 | 0 | 0 | 10 | 9 | 0 | 0 | 15 | 4 | 1 | 0 | 16 | 3 | 1 | 0 |
| | 6 | 18 | 2 | 0 | 0 | 19 | 1 | 0 | 0 | 16 | 2 | 0 | 0 | 17 | 0 | 0 | 0 | 18 | 2 | 0 | 0 | 18 | 0 | 1 | 0 |
| | 7 | 19 | 1 | 0 | 0 | 20 | 0 | 0 | 0 | 17 | 2 | 1 | 0 | 15 | 5 | 0 | 0 | 20 | 0 | 0 | 0 | 14 | 4 | 2 | 0 |
| | 8 | 15 | 3 | 0 | 1 | 20 | 0 | 0 | 0 | 17 | 2 | 0 | 0 | 19 | 0 | 0 | 0 | 17 | 2 | 0 | 0 | 20 | 0 | 0 | 0 |
| 5 | 1 | 9 | 10 | 1 | 0 | 10 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 9 | 6 | 2 | 3 | 11 | 5 | 0 | 5 | 11 | 4 | 0 |
| | 2 | 17 | 2 | 0 | 0 | 19 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 10 | 0 | 0 | 8 | 11 | 0 | 0 | 12 | 8 | 0 | 0 |
| | 3 | 15 | 5 | 0 | 0 | 14 | 6 | 0 | 0 | 16 | 4 | 0 | 0 | 1 | 7 | 4 | 5 | 4 | 14 | 2 | 0 | 7 | 12 | 1 | 0 |
| | 4 | 12 | 7 | 0 | 0 | 7 | 11 | 1 | 0 | 11 | 8 | 0 | 0 | 2 | 4 | 3 | 11 | 2 | 3 | 9 | 6 | 6 | 6 | 6 | 2 |
| | 5 | 16 | 4 | 0 | 0 | 15 | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 16 | 3 | 0 | 1 | 17 | 2 | 0 | 0 | 16 | 4 | 0 | 0 |
| | 6 | 20 | 0 | 0 | 0 | 19 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 4 | 0 | 0 | 19 | 1 | 0 | 0 | 17 | 3 | 0 | 0 |
| | 7 | 20 | 0 | 0 | 0 | 17 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 18 | 0 | 1 | 0 | 18 | 1 | 0 | 0 | 18 | 2 | 0 | 0 |
| | 8 | 20 | 0 | 0 | 0 | 18 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 19 | 1 | 0 | 0 | 19 | 1 | 0 | 0 | 17 | 2 | 0 | 0 |
| 6 | 1 | 5 | 14 | 1 | 0 | 6 | 13 | 0 | 0 | 7 | 13 | 0 | 0 | 2 | 8 | 10 | 0 | 4 | 12 | 4 | 0 | 3 | 15 | 2 | 0 |
| | 2 | 18 | 2 | 0 | 0 | 18 | 2 | 0 | 0 | 17 | 3 | 0 | 0 | 10 | 10 | 0 | 0 | 14 | 6 | 0 | 0 | 13 | 7 | 0 | 0 |
| | 3 | 5 | 14 | 0 | 0 | 13 | 7 | 0 | 0 | 8 | 11 | 1 | 0 | 7 | 6 | 5 | 2 | 2 | 13 | 4 | 1 | 2 | 18 | 0 | 0 |
| | 4 | 5 | 14 | 1 | 0 | 0 | 15 | 5 | 0 | 0 | 0 | 0 | 0 | 2 | 4 | 12 | 2 | 0 | 14 | 6 | 0 | 4 | 10 | 6 | 0 |
| | 5 | 15 | 5 | 0 | 0 | 16 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 10 | 1 | 1 | 11 | 8 | 0 | 0 | 6 | 13 | 1 | 0 |
| | 6 | 19 | 1 | 0 | 0 | 19 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 17 | 3 | 0 | 0 | 18 | 1 | 0 | 0 | 18 | 2 | 0 | 0 |
| | 7 | 18 | 2 | 0 | 0 | 17 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 9 | 0 | 0 | 14 | 5 | 1 | 0 | 15 | 5 | 0 | 0 |
| | 8 | 18 | 2 | 0 | 0 | 15 | 4 | 0 | 0 | 16 | 4 | 0 | 0 | 18 | 2 | 0 | 0 | 19 | 1 | 0 | 0 | 19 | 1 | 0 | 0 |

**Table 3.** Components of variance for the potato damage data

| Interaction term | component (s.e.) |
|---|---|
| rod.energy | 0.120 (0.073) |
| rod.variety | 0.074 (0.031) |
| rod.weightclass | 0.042 (0.022) |
| energy.variety | 0.003 (0.010) |
| energy.weightclass | 0.013 (0.016) |
| variety.weightclass | 0.011 (0.011) |
| rod.energy.variety | 0.039 (0.023) |
| rod.energy.weightclass' | - |
| rod.variety.weightclass' | - |
| energy.variety.weightclass' | - |
| rod.energy.variety.weightclass | 0.055 (0.024) |

' Negative estimates (are replaced by 0.0001).

corresponding components of variance. Normal distributions were assumed with residual variance $\nu^2 = 1$. Four-factor-interaction effects were absorbed when solving mixed model equations (8). Estimated cutpoints (standard errors in parentheses) are 0 (fixed), 1.41 (0.03) and 2.30 (0.04). Estimated components of variance are shown in Table 3. Estimated rod effects as differences with rod number one are:

| Rod: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| | 0 | -1.26 | -0.42 | 0.55 | -1.50 | -1.85 | -1.76 | -2.09. |

Standard errors of differences are approximately 0.43. Estimates in Table 3 show that the larger components involve interactions with rods. Estimated rod effects are therefore less precise than e.g. estimated variety effects (standard error of difference about 0.20). Despite the larger standard errors it may be concluded e.g. that rods 1, 2, 3, 4 are worse than rod 8.

## 6 Extending the threshold model

So far residuals were assumed to follow a normal distribution, corresponding to a probit link for probabilities $P(y_i \leq j \mid \mathbf{u}) = \psi_{ij}$. Other popular choices are the logistic distribution and extreme value distribution. For the logistic distribution, with $\nu^2 = \pi^2/3$, the link function is the logit link:

$$\text{logit}(\psi_{ij}) = \log(\psi_{ij}/(1-\psi_{ij})) = \theta_j - \eta_i.$$

For the extreme value distribution, with $\nu^2 = 1$, the link function is the complementary log-log link:

$$\log(-\log(1-\psi_{ij})) = \theta_j - \eta_i.$$

These alternatives, for models with fixed effects only, are discussed in some detail by McCullagh (1980) and referred to as the *proportional odds* and *proportional hazards model* respectively.

We will now introduce more general link functions, or underlying distributions, allowing for additional unknown (shape) parameters. Let the cdf of the underlying variable z from (7), conditional upon the random effects $\mathbf{u}$, be $F((z-\eta)/\nu; \lambda)$, where $\lambda$ is a vector of additional shape parameters. Let $f(x) = F'(x; \lambda)$ be the derivative with respect to x. A useful family of distributions, as a robust alternative to the standard normal distribution, is the family of Student distributions: $f(x) = \sqrt{(\lambda/(\lambda-2))} f_\lambda(\sqrt{(\lambda/(\lambda-2))}x)$, for $\lambda > 2$ and $f(x) = f_\lambda(x)$ for $0 < \lambda \leq 2$, where $f_\lambda(.)$ is the pdf of Student's distribution with $\lambda$ degrees of freedom. For use of the Student distribution in statistical inference see e.g. Fraser (1979). Usually $\eta$ and $\nu^2$ will be the (conditional) mean and variance of z, although these moments do not necessarily have to exist, e.g. for the Cauchy distribution (Student distribution with $\lambda = 1$) where $f(x) = 1 / \{\pi(1+x^2)\}$. Typically $\lambda$ is assumed not to depend on the experimental units.

In addition to $\eta$, $\nu^2$ may be modelled in terms of explanatory variables as well:

$$g(\nu^2) = \eta_\nu = \mathbf{X}_\nu \boldsymbol{\gamma}.$$

Here, g(.) and $\eta_\nu$ are the link function and linear predictor for the variance. $\mathbf{X}_\nu$ is a design matrix and $\boldsymbol{\gamma}$ a vector of fixed effects for the variance. An obvious choice for g(.) is the logarithmic link, see e.g. Aitkin (1987) and McCullagh and Nelder (1989, §5.2.2 and Ch.10).

Extra shape parameters are added to vector $\boldsymbol{\xi}$ and estimating equations are derived once again by Pregibon's method. Derivatives in $\mathbf{X}_\xi$ can be evaluated using the following results:

$$\partial h_{ij}(\eta_i; \boldsymbol{\xi})/\partial \xi_k = N_i\{(\partial F(\theta^*_{ij}; \lambda)/\partial \xi_k) - (\partial F(\theta^*_{i\,j-1}; \lambda)/\partial \xi_k)\},$$

$$\partial h_{ij}(\eta_i; \boldsymbol{\xi})/\partial \eta_i = N_i\{f(\theta^*_{i\,j-1}; \lambda) - f(\theta^*_{ij}; \lambda)\} / \nu_i.$$

Consider for example parameters $\boldsymbol{\gamma}$ in the variances $\nu_i^2$:

$$\partial F(\theta^*_{ij}; \lambda)/\partial \gamma_k = (\partial F(\theta^*_{ij}; \lambda)/\partial \nu_i^2)(\partial \nu_i^2/\partial \eta_{\nu\,i})(\partial \eta_{\nu\,i}/\partial \gamma_k) = -\tfrac{1}{2} f(\theta^*_{ij}; \lambda)\, \theta^*_{ij}\, x_{\nu\,i,k} / \{g'(\nu_i^2)\, \nu_i^2\}.$$

For the log link, elements of $\mathbf{X}_\xi$ are of the form:

$$\tfrac{1}{2}x_{\nu\, i,k}\ \{f(\theta^*_{ij};\ \lambda)(\theta_j-\mu_i)-f(\theta^*_{i\,j-1};\ \lambda)(\theta_{j-1}-\mu_i)\}/\{f(\theta^*_{ij};\ \lambda)\ -\ f(\theta^*_{ij-1};\ \lambda)\}.$$

For a single shape parameter $\lambda$, it may be more convenient to fit the model for a grid of values for $\lambda$, and inspect the results. For the cutpoints, the following reparameterisation may be convenient: $\theta_1 = 0$, $\theta_2 = \exp(\delta_1)$, $\theta_3 = \exp(\delta_1) + \exp(\delta_2)$, ... . Elements for $\delta_k$ in $\mathbf{X}_\xi$ are of the form: $f(\theta^*_{ij};\ \lambda)\ \exp(\delta_{j-1})\ /\ \{f(\theta^*_{ij};\ \lambda)\ -\ f(\theta^*_{i\,j-1};\ \lambda)\}$, when $1 \le k = j\text{-}1$, or $\exp(\delta_k)$, when $1 \le k < j\text{-}1$, and 0 otherwise.

**Table 4.** Results of 50 simulations

Results for treatment contrasts on the underlying scale:

| | | $\nu = 1$ | | | $\nu$ free | | |
|---|---|---|---|---|---|---|---|
| Contrast | True value | Average of sims. | s.d. | Average s.e. | Average of sims. | s.d. | Average s.e. |
| 2-1 | 0 | 0.09 | 0.23 | 0.21 | -0.01 | 0.36 | 0.35 |
| 3-1 | 1 | 0.79 | 0.13 | 0.21 | 1.04 | 0.19 | 0.25 |
| 4-1 | 1 | 0.69 | 0.17 | 0.21 | 1.01 | 0.32 | 0.37 |

Results for estimated $\nu_i$'s ($\nu_1$ fixed at 1):

| Treatment | True value | Average | s.d. | Average s.e. |
|---|---|---|---|---|
| 2 | 2 | 2.02 | 0.36 | 0.40 |
| 3 | 1 | 1.00 | 0.21 | 0.19 |
| 4 | 2 | 1.98 | 0.42 | 0.42 |

To illustrate the scope for improvement obtained by simultaneous modelling of $\eta$ and $\nu^2$, a modest simulation was carried out. Data was generated from four normal distributions, representing e.g. four treatments. Combinations of $\eta$ and $\nu$ were (1, 1), (1, 2), (2, 1) and (2, 2) respectively. The sample size was 50 in each case. Cutpoints were -1, 0, 1 and 2. Estimated differences in means with respect to treatment 1 for homogeneous $\nu^2$ (fixed at value 1) and for heterogeneous $\nu^2$ ($\nu^2$ fixed at value 1 for treatment 1 and estimated for treatments 2, 3 and 4) are presented in Table 4. In the table average differences over 50 simulations, corresponding standard deviations as estimated from the 50 simulations and the average of the 50 standard errors for the treatment contrasts produced by Genstat are shown. The latter standard errors are based on Fisher information under normality for the

adjusted dependent variate. Estimated treatment contrasts are seen to be fairly unbiased when heterogeneity is taken into account. Note that the standard deviations estimated from the 50 simulations and the averages of the standard errors from Genstat are in reasonable agreement. Also shown are some results for the estimated v's. Again, estimates are fairly unbiased and estimated standard errors on average are quite acceptable. We will look at three examples of the extended model.

## 7 Therapeutic effect of nootropic agents

This example is from Uesaka (1993), who used it for illustrating a test for interaction between two treatments and a block factor based on logarithmic generalised odds ratios. The data is from a multicenter trial on the therapeutic effect of two nootropic agents on patients with multi-infarct disease. The effect was evaluated on an ordinal scale of five categories and patients were classified a posteriori into four groups according to the baseline severity of overall neurological symptoms. Likelihood ratio test statistics (which may be referred to an appropriate chi-square distribution) for treatment effects and interaction, for different underlying distributions fitted to the fixed effects model are presented in Table 5, along with the residual deviance as a measure of goodness of fit.

**Table 5.** Therapeutic effect of nootropic agents. Likelihood ratio statistics for treatment main effects and interaction and mean deviances for various models fitted to the data

| Distribution | Likelihood ratio statistics | | Mean deviance |
|---|---|---|---|
| | Main effects (1 df) | Interaction (3 df) | |
| normal | 3.0 | 4.4 | 0.85 |
| logistic | 2.5 | 4.7 | 0.88 |
| extreme value | | | |
| left skew | 2.7 | 4.4 | 1.19 |
| right skew | no convergence | | |
| lognormal | 2.3 | 4.0 | 0.85 |
| Student | converges to the normal distribution (df = ∞) | | |
| 1 df | no convergence | | |
| 2 df | 1.6 | 4.8 | 1.00 |
| 3 df | 1.9 | 4.8 | 0.96 |
| 5 df | 2.3 | 4.8 | 0.91 |
| 8 df | 2.5 | 4.7 | 0.88 |
| 20 df | 2.8 | 4.5 | 0.86 |

This illustrates that there is little evidence for the existence of a treatment main effect or interaction between treatment and baseline severity. Use of the normal distribution may indicate a treatment effect, but this effect is not robust for the choice of underlying distribution.

## 8 Severity of nausea in chemotherapy

Data on the severity of nausea (in 6 ordered categories from "none" to "severe") experienced by 219 patients with cancer while undergoing chemotherapy, is taken from Farewell (1982). Patients were classified as to whether their chemotherapy included or did not include cisplatin. Farewell introduces overdispersion by allowing a random shift of the cutpoints for each patient. Within a patient all $\theta$'s are shifted by the same amount, i.e. shifts can also be considered as random main effects u for patients. Farewell starts with a proportional hazards model and conveniently assumes that exp(u) is from a gamma distribution. This allows the u's to be integrated out of the probabilities $\pi$ for severity of nausea. The likelihood is optimized over a grid of values of the index parameter c of the gamma distribution. The mean deviance for the extreme value distribution, without the u's ($c = \infty$), is 2.91 on 4 degrees of freedom (10 parameters for the saturated model minus 6 for the threshold model) and the proportional hazards model is rejected at the 0.05 level employing the likelihood ratio test with a chi-square distribution on 4 degrees of freedom. For the normal distribution the mean deviance is 1.99, for the logistic distribution: 1.65 and for the Student distribution with $\lambda = 1$ (Cauchy distribution): 0.45. Neither distribution leads to rejection of the model by the likelihood ratio test on either 3 or 4 degrees of freedom at the 0.05 level. For Farewells model with random shifts ($\hat{c} = 1$), the mean deviance is 1.60 on 3 degrees of freedom. The ratios of the ML estimates for the cisplatin effect $\hat{\beta}$ and its estimated standard error (ignoring variability in additional paramaters, i.e. $\lambda$ for the Student distribution and c for Farewell's model) on the underlying scale for the Student ($\lambda = 1$), normal and logistic distribution and Farewell's overdispersion model are 3.6, 3.3, 3.3 and 3.9 respectively. Although Farewell did not intend to present a general model for ordinal data, and only used the example as an illustration of the random shift model, it can be concluded that an improved fit can just as easily be obtained by a change of residual distribution (or link function for cumulative probabilities) as by introduction of variability in the cutpoints. Note that when patient and residual effects on the underlying scale are from the normal distribution, they can be pooled and the model remains essentially the same. A similar result approximately holds for normal and logistic effects as well.

## 9 Damage to potato tubers, continued

As a point of interest the assumption of a common residual variance on the underlying scale was checked. Adding dependence of $\nu^2$ on type of rod results in the following estimates for $\nu$: 1 (fixed), 0.90 (0.06), 0.86 (0.05), 0.76 (0.04), 0.89 (0.07), 1.09 (0.09), 0.85 (0.07) and

1.00 (0.10) for rods 1 to 8 respectively (standard errors in parentheses). Comparisons may be made on the log scale. However, allowing for heterogeneity does not entail important changes in conclusions about the differences between rods.

## 10 Discussion

McCullagh (1980) discusses the fixed effects threshold model. Thompson and Baker (1981) show how these models can be fitted into the GLM framework for ML estimation. ML estimation for threshold models with normal random effects, employing numerical integration by Gauss-Hermite quadrature (Abramowitz and Stegun, 1965, p.924), is presented in e.g. Jansen (1990, 1992). Iterative re-weighted REML is more akin to quasi-likelihood estimation. Estimation only depends on the first two moments and no full distributional assumptions are needed. When for grouped data the residual variance in the mixed model for the adjusted dependent variate is not kept at a fixed value, it may represent an additional multiplicative under- or overdispersion parameter with respect to the covariance matrix of the multinomial distribution (McCullagh and Nelder, 1990, §5.5). Application of GLMM methodology to the one-threshold model (J = 1) for binomial data is discussed in Engel, Buist and Visscher (1995). They show that the estimate for the additional dispersion parameter may be expressed in terms of Pearson's chi-square statistic evaluated for predicted random effects with an "effective" number of degrees of freedom estimated from the data.

In the context of animal breeding, Gianola and Foulley (1983) present a Bayesian approach to inference about $\boldsymbol{\beta}$, $\mathbf{u}$ and $\boldsymbol{\theta} = (\theta_1 \ldots \theta_{J-1})'$ for known components of variance. The aim is to evaluate animals on the basis of their predicted genetic merit $\hat{\mathbf{u}}$. Thresholds and fixed effects are nuisance parameters. Vague priors for $\boldsymbol{\theta}$ and $\boldsymbol{\beta}$ and a normal prior density for $\mathbf{u}$ are assumed. $\boldsymbol{\beta}$, $\mathbf{u}$ and $\boldsymbol{\theta}$ are estimated by the mode of their joint posterior density, i.e. by the values that maximize the joint pdf of $\mathbf{y}$ and $\mathbf{u}$. Maximization is by Fisher scoring. Some algebra shows that this is equivalent to the use of equations (8) extended with the covariates in $\mathbf{X}_\xi$ for $\Delta\boldsymbol{\xi} = \Delta\boldsymbol{\theta}$ as following from Pregibon's correction. The Bayesian procedure presented in Harville and Mee (1984) is equivalent to Gianola and Foulley (1983), but also includes estimation of components of variance. See in this respect also Foulley, Im, Gianola and Hoeschele (1987). An update of the components of variance can be shown to correspond to one step of an EM algorithm for conventional mixed models applied to the adjusted dependent variate $\zeta$, see e.g. Engel, Buist and Visscher (1995). This solves the same set of final estimating equations as the Fisher scoring algorithm for REML employed in this paper.

Optimization of the joint pdf of $\mathbf{y}$ and $\mathbf{u}$ is the basic principle behind the estimation procedure suggested by McGilchrist (1994). McGilchrist presents three possible estimators for the components of variance referred to as: BLUP, ML and REML estimators. The REML estimators are of the EM type, similar to estimation of the components in Harville

and Mee (1984) and Foulley, Im, Gianola and Hoeschele (1987), and equivalent to the IRREML estimators.

For normally distributed random effects **u**, IRREML estimates $\hat{\boldsymbol{\beta}}$ and predictions $\hat{\mathbf{u}}$ are maximum hierarchical likelihood estimates, according to the definition by Lee and Nelder (1996) of hierarchical likelihood (h-likelihood) as the logarithm of the joint pdf of **y** and **u**. Use of the h-likelihood is motivated by Laplace integration. For Laplacian integration in nonlinear mixed models see also Wolfinger (1993) and for GLMMs Breslow and Clayton (1993). In the discussion of Lee and Nelder's paper, the relationship between maximum h-likelihood and ML estimation is commented upon by Engel and Keen (1996). These comments include estimation of components of variance by maximum adjusted profile h-likelihood estimation in relation to ML estimation, and cover the present case of ordinal data as well.

Estimation as presented in Gilmour, Anderson and Rae (1987) is a generalization of their approach for one-threshold models (Gilmour, Anderson and Rae, 1985) for an underlying standard normal distribution. There is a strong similarity to IRREML, except that their adjusted dependent variate and weights are expressed in terms of marginal rather than conditional moments with respect to u. A comparison, which includes extensive simulation results, between the marginal and conditional approaches for the one-threshold model is presented in Engel, Buist and Visscher (1995). The example about foot shape in lambs in Section 4 offers a numerical comparison.

Since the fixed effects $\boldsymbol{\beta}$ are introduced on the same underlying scale as the random effects **u**, the model is *subject specific* in the terminology of Zeger, Liang and Albert (1988). The interpretation of effects $\boldsymbol{\beta}$ is in terms of conditional probabilities and not in terms of marginal probabilities. The latter follow by integrating out the random effects. In the threshold model, with F(.) equal to the cdf of the normal distribution, $v^2 = 1$ and $\mathbf{u} \sim N(\mathbf{0}, \mathbf{G})$, marginal effects on the probit scale follow by shrinking elements of $\boldsymbol{\beta}$ by a factor $(1+\sigma_1^2+...+\sigma_c^2)^{-½}$. When F(.) is the cdf of the standard logistic distribution and $v^2 = \pi^2/3$, for the marginal probabilities, the logit scale holds only approximately, and an approximate shrinkage factor may be derived from the close connection between the normal and logistic distribution, see e.g. Engel, Buist and Visscher (1995). In general, expressions for marginal effects may be derived by Taylor series expansion, see Engel and Keen (1994).

Approximation by Laplace integration is not sufficiently accurate for estimation of components of variance when the amount of information per individual random effect is low, irrespective of the number of random effects. Simulation results in Engel, Buist and Visscher (1995) show that in that case IRREML does not perform well for the one-threshold model for binary data. A similar result can be expected for thresholds models for ordinal data. The chemotherapy data in Section 8 offer an extreme example. The threshold model with an underlying extreme value distribution for the residuals and random normal patient effects is, in view of the similarity between the lognormal and the gamma distribution, an obvious contender to Farewell's random shift model. IRREML produces an

estimated cisplatin effect of 0.32, with an estimated standard error of 0.20. This suggests that cisplatin has no significant effect, in contrast to the various models fitted in Section 8, which is undoubtedly a consequence of the fact that to each shift u there corresponds only one ordinal observation. When the u's are integrated out, resulting in a link function with additional index parameter c, the algorithm from Section 2 can be applied.

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# Chapter 8

## Bias reduction of heritability estimates in threshold models

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The simulation study from Chapter 6 for threshold models for binary data is extended and two methods for bias-correction are studied.

# Bias reduction of heritability estimates in threshold models

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**Summary** Penalized quasi-likelihood and iterated re-weighted REML estimates for heritability (or intra-class correlation) in threshold models for binary data with extra random components can be seriously biased. Recent approaches to correct for this bias are studied by simulation, with emphasis on animal breeding models for binary data. Scope for reduction of bias is found to be slim, because of the commonly large number of fixed effects in animal breeding models. Minimal dimensions for the data are identified, such that bias and root mean squared error are of modest size, and useful inference on heritability (or intra-class correlation) is feasible.

**Keywords**: binary data, threshold model, heritability, bias, mixed model, REML, PQL

## 1 Introduction

A threshold model for binary or binomial data with fixed and random effects and associated components of variance can also be presented in the form of a generalized linear mixed model (GLMM) or a hierarchical generalized mixed model (HGLM). General estimation procedures for GLMMs and HGLMs proposed by Schall (1991), Breslow and Clayton (1993) (penalized quasi-likelihood or PQL), Engel and Keen (1994) (iterated re-weighted REML or IRREML), McGilchrist (1994) (the method referred to as the REML approach) and Lee and Nelder (1996) (maximum adjusted profile h-likelihood or MAPHL), and the Bayesian maximum a posteriori (MAP) approach proposed by Gianola and Foulley (1983) and Harville and Mee (1984) are equivalent for threshold models for binary data (see Engel, Buist and Visscher, 1995; Keen and Engel, 1996). All these methods avoid the problem of high dimensional numerical integration in evaluation of the likelihood (or a posterior distribution). Basically, all of them, implicitly or explicitly, involve a normal approximation of the distribution of the random effects conditional upon the observations, which can be motivated by Laplace integration, see Lee and Nelder (1996), Engel and Keen (1996) and for MAP: Foulley, Im, Gianola and Hoeschele (1987). That the same estimating equations

can be derived in many different ways suggests that MAP / PQL / IRREML / MAPHL is a proper method for estimation of components of variance, intra-class correlation or heritability in threshold models for binary data. Unfortunately, simulation studies (e.g. Gilmour, Anderson and Rae, 1985; Engel et al., 1995) show that estimates so obtained can be seriously biased. Gilmour et al. (1985) were the first to observe bias problems. They studied a simple one-way model, e.g. a sire model with unrelated sires, with m offspring per sire, and with a binary observation per offspring. On the underlying scale, normal distributions were assumed for the independent genetic sire effects and the residual effects, with an overall mean as the only fixed effect. The simulation results suggest that with MAP / PQL / IRREML / MAPHL the sire variance is underestimated approximately by a factor (m-1) / m, irrespective of the number of sires. Informal arguments for this factor are given in Thompson (1990) and Engel et al. (1995). In more realistic models with more fixed effects and varying family sizes, bias is of a more complex nature, and positive bias may occur as well, depending on the number of observations per fixed effect, as found by Engel et al. (1995).

For small family sizes (small numbers of binary observations per random effect, in a more general formulation), variance and heritability estimates may seriously err, even when the number of families (the number of random effects) is very large. Reduction of this bias is paramount in animal breeding, where a poor heritability estimate will give a wrong impression of potential genetic gain under selection and may affect estimated breeding values (i.e. predictions for individual genetic random effects used in selection). Breslow and Lin (1995) proposed a bias correction for PQL estimates for a variance component in GLMMs. In this paper the performance of this correction applied to heritability estimates in a sire model for binary data is studied by simulation and compared with another method, presented in Engel et al. (1995), based on a change of iterative weights in IRREML. Minimal dimensions are identified for the data, such that useful inference on heritability or intra-class correlation is feasible.

## 2 Bias correction

Although, for convenience, notation for a sire model is adopted, the formulae presented apply to an animal model (see e.g. Henderson, 1984, Ch.22) with a general additive relationship matrix as well. Vector $\mathbf{r}$ of values for the *liability* on the underlying scale is expressed as:

$$\mathbf{r} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \boldsymbol{\epsilon} = \boldsymbol{\eta} + \boldsymbol{\epsilon}. \qquad (1)$$

Here, $\boldsymbol{\beta}$ and $\mathbf{u}$ are vectors of p fixed effects (for e.g. combinations of herds, years and seasons: HYS effects) and q random sire effects, respectively. $\mathbf{u} \sim N(\mathbf{0}, \mathbf{A}\sigma_S^2)$, where $\mathbf{A}$ is

the (known) additive genetic relationship matrix and $\sigma^2_S$ is the (unknown) sire component of variance. **X** and **Z** are design matrices. $\eta$ is the linear predictor in the corresponding GLMM. Independent residuals in vector $\epsilon$ follow a standard normal distribution. A positive value for the liability of an offspring of a sire corresponds to an observation y = 1, and a negative value to y = 0. Conditional upon sire effects, mean and variance are: $E(y \mid \mathbf{u}) = \mu$ and $Var(y \mid \mathbf{u}) = V(\mu) = \mu(1-\mu)$, where $\mu$ is a conditional probability for e.g. an offspring to be alive at a certain age in a mortality study, denoted by $\mu_{ij}$ for the j-th offspring of the i-th sire, and V(.) is the (conditional) variance function.

The bias correction factor in Breslow and Lin (1995) is derived for small values of the variance component for a GLMM with a canonical link function and independent normally distributed random effects. For a sire model for binary data this implies a logistic distribution for the residuals, i.e. cdf $L(\varepsilon) = 1 / (1+\exp(-\varepsilon))$, and normal genetic effects for unrelated sires, i.e. **A** is an identity matrix. To extend the correction factor to related sires, the random part **Zu** of (1) is written as: $(\mathbf{ZL})(\mathbf{L}^{-1}\mathbf{u}) = \tilde{\mathbf{Z}}\tilde{\mathbf{u}}$. **L** is a lower triangular matrix such that $\mathbf{LL}' = \mathbf{A}$, see Quaas (1976) and Henderson (1976). Elements of $\tilde{\mathbf{u}}$ are independent and we just have to replace design matrix **Z** by $\tilde{\mathbf{Z}}$ in expressions for the correction factor. The corrected variance estimator is: $\hat{\sigma}^2_{S,corr} = f\,\hat{\sigma}^2_S$, where $\hat{\sigma}^2_S$ is the MAP / PQL / IRREML / MAPHL estimator, and factor f follows from:

$$f = a / (a+b), \qquad (2)$$

where

$$a = \mathbf{1}_q'(\mathbf{L}'\mathbf{Z}'\mathbf{W}_0\mathbf{ZL})^{(2)}\,\mathbf{1}_q / 2 = \text{trace}(\mathbf{Z}'\mathbf{W}_0\mathbf{ZAZ}'\mathbf{W}_0\mathbf{ZA}) / 2$$

and

$$b = [\mathbf{1}_q'(\mathbf{L}'\mathbf{Z}')^{(2)}\{\mathbf{W}_2 - \mathbf{W}_1\mathbf{X}(\mathbf{X}'\mathbf{W}_0\mathbf{X})^{-1}\mathbf{X}'\mathbf{W}_1\}(\mathbf{ZL})^{(2)}\,\mathbf{1}_q] / 4.$$

$\mathbf{1}_q$ denotes a q x 1 vector of ones. For any matrix **M** with elements $m_{ij}$, $\mathbf{M}^{(2)}$ is the matrix with elements $m^2_{ij}$, i.e. the direct (Hadamard) product of **M** with itself. $\mathbf{W}_0$, $\mathbf{W}_1$ and $\mathbf{W}_2$ are diagonal matrices with elements $\mu_{0,ij}(1-\mu_{0,ij})$, $\mu_{0,ij}(1-\mu_{0,ij})(1-2\mu_{0,ij})$ and $\mu_{0,ij}(1-\mu_{0,ij})(6\mu^2_{0,ij}-6\mu_{0,ij}+1)$, respectively. $\mu_{0,ij}$ is $\mu_{ij}$ evaluated for the estimated fixed effects and sire effects replaced by 0, i.e. $\mu_0 = (1+\exp(-\mathbf{X}\hat{\boldsymbol{\beta}}))^{-1}$ for logistic residuals. To a close approximation (Johnson and Kotz, 1970, p6): $L(ct) = \Phi(t)$, where $\Phi$ is the cdf of the standard normal distribution, and $c = (15/16)\pi/\sqrt{3}$. This implies that (2) approximately holds for normal residuals as well, with $\mu_0 = \Phi(\mathbf{X}\hat{\boldsymbol{\beta}})$.

In the simple sire model of Gilmour et al. (1985), discussed in the introduction, $a = qm^2\mu_0^2(1-\mu_0)^2/2$, $b = -qm\mu_0^2(1-\mu_0)^2/2$ and $f = a / (a+b) = m / (m-1)$, which is an encouraging result. For a more realistic model we take resort to simulation, extending studies reported in Hoeschele and Gianola (1989) and Engel et al. (1995), involving an unbalanced sire model for binary data with a relatively large number of fixed effects. Sire effects and residual effects are generated from normal distributions, since this is a more familiar choice than the combination of normal and logistic distributions.

In Engel et al. (1995) use of the following alternative iterative weights in IRREML is suggested:

$$w_0 = \{g'(\mu)^2 \, E(V(\mu))\}^{-1}, \qquad (3)$$

where g′ is the derivative of the link function g.

Both from the corrected component $\hat{\sigma}^2_{S,corr}$ and from the IRREML estimate with weights $w_0$, estimated heritabilities will be calculated. For a sire model the heritability $h^2$ is:

$$h^2 = 4 \, \sigma^2_S / (\sigma^2_S+1) = 4\rho,$$

where $\rho$ is the intra-class correlation on the underlying scale.

## 3 The simulated data

The fixed HYS effects are initially sampled from a $N(0, \sigma^2_{HYS})$ distribution. For each HYS combination a sire has 0, 1 or 2 offspring with probabilities 1 - $p_{HYS}$, $p_{HYS}$ / 2 and $p_{HYS}$ / 2 respectively. Values for $p_{HYS}$ are 0.025, 0.05, 0.10, 0.20, 0.25 and 0.30. The HYS effects and design for sires and offspring are generated only once, after which the same HYS values and the same design are used in all subsequent simulations. Other fixed effects are sire group effects: 4 groups with effects -0.40, -0.15, 0.15 and 0.40. The number of fixed effects p is either 139 (= 135 HYS + 4 sire groups), 38 (= 34 + 4) or 1 (just an overall mean). Independent sire effects are sampled from a $N(0, \sigma^2_S)$ distribution, where $\sigma^2_S = h^2/(4-h^2)$ and $h^2 = 0.25$. The number of sires q is either 50 (12, 14, 13 and 11 for the sire groups) or 200 (48, 56, 52 and 44 for the sire groups). For p = 139 fixed effects, simulation results for q = 100 sires (24, 28, 26 and 22 for the sire groups) were collected as well. Residuals are from a N(0, 1) distribution. The overall constant on the underlying scale is: $-\Phi^{-1}(P_0) (1+\sigma^2_{HYS}+\sigma^2_S)^{0.5}$, where $P_0 = 0.90$ is the overall incidence. The proportion of variance explained by the HYS effects, $\sigma^2_{HYS} / (1+\sigma^2_{HYS}+\sigma^2_S) = \sigma^2_{HYS} / (\sigma^2_{HYS}+(4/(4-h^2)) = 0.30$ for $h^2 = 0.25$. Calculations are performed with Genstat 5 (1993), employing procedure IRREML (Keen, 1994). Expression (2) simplifies, since for the simulation

$$a = \sum_i \{\sum_j \mu_{o,ij}(1-\mu_{0,ij})\}^2 / 2 \text{ and } b = [\sum_i \sum_j \mu_{0,ij}(1-\mu_{0,ij})(6\mu^2_{0,ij}-6\mu_{0,ij}+1) - \mathbf{d}'\mathbf{X}(\mathbf{X}'\mathbf{W}_0\mathbf{X})^{-1}\mathbf{X}'\mathbf{d}] / 4,$$

where $\mathbf{d}$ is a vector with elements $\mu_{0,ij}(1-\mu_{0,ij})(1-2\mu_{0,ij})$. The alternative weights from (3) are:

$$w_0 = \phi(\eta)^2 / \{P(1-P) - \rho \, \phi(\eta_*)^2\},$$

where $\phi$ is the pdf of the standard normal distribution, $P = P(y=1) = \Phi(\eta_*)$ is the marginal probability and $\eta^* = \mathbf{x}'\boldsymbol{\beta} / \sqrt{(1+\sigma^2_S)}$ is the marginal linear predictor.

## 4 Simulation results

Simulation results for heritability based on 200 runs for each parameter configuration are shown in Table 1. Results without correction (bold face in the table) will be discussed first. Within each column, when the average number m of observations (offspring) per random effect (sire) increases (going from bottom to top in the table), the absolute bias and root mean squared error decrease. The bias vanishes, which agrees with consistency for p and q fixed and $m \to \infty$. Within a row, when the number of fixed effects q is reduced from 139 to 38 to 1, or the number of sires p is increased from 50 to 200, the bias starts with a

**ble 1** Simulation results for heritability. Bias and root mean squared error are expressed as a percentage of the true value. ults in the form: bias (s.e. bias) / root mean squared error. First line is the uncorrected result (bold face), second line is the lt after use of the correction factor, third line is the result with the alternative weights. Heritability $h^2 = 0.25$. Incidence $P_0$ = ). Number of fixed effects p is 139, 38 or 1. Number of sires q is 50, 100 (p = 139 only) or 200. Number of offspring per sire 1, 51, 41, 20, 10, 5 ($p_{HYS}$ = 0.30, 0.25, 0.20, 0.10, 0.05, 0.025). The total number of observations within a row is about the e for the same number of sires, e.g. in the first row for q = 50 both for p = 139, 38 and 1: m = 60.75.

| ber of d HYS cts p | 139 fixed effects | | | 38 fixed effects | | overall fixed constant only | |
|---|---|---|---|---|---|---|---|
| ber of s q | 50 sires | 100 sires | 200 sires | 50 sires | 200 sires | 50 sires | 200 sires |
| ber of spring sire m ) | | | | | | | |
| | **14.5 (3.6)/ 52.2** | **5.1 (2.0)/ 28.7** | **-2.1(1.4)/ 19.2** | **0.5 (3.1)/ 44.1** | **-4.2(1.2)/ 18.0** | **-4.2(2.5)/ 35.3** | **-4.9(1.2)/17.0** |
| 0) | 17.8 (3.6)/ 54.5 | 7.8 (2.1)/ 30.0 | 0.4(1.4)/ 19.5 | 3.2 (3.2)/ 45.3 | -1.9(1.3)/ 18.0 | -2.8(2.5)/ 35.7 | -3.5(1.2)/16.8 |
| | 1.1 (3.1)/ 44.3 | -3.6 (1.7)/ 24.7 | -7.8(1.2)/ 18.5 | -7.8 (2.8)/ 39.6 | -8.4(1.1)/ 17.8 | -12.3(2.1)/ 31.9 | -11.8(1.0)/18.3 |
| | **15.0 (3.7)/54.1** | **5.9 (2.1)/ 30.2** | **-1.7(1.4)/ 20.1** | **-6.2 (2.9)/ 40.7** | **-5.4(1.4)/ 20.2** | **-6.9(2.6)/ 37.0** | **-9.1(1.2)/18.6** |
| 5) | 18.7 (3.8)/56.7 | 9.3 (2.2)/ 32.5 | 1.3(1.5)/ 20.6 | -3.1 (2.9)/ 41.6 | -2.4(1.4)/ 20.2 | -5.2(2.6)/ 37.4 | -7.4(1.2)/18.1 |
| | 3.6 (3.2)/45.1 | -2.4 (1.8)/ 25.6 | -6.1(1.3)/ 18.6 | -12.8 (2.6)/ 38.4 | -6.7(1.3)/ 18.8 | -13.2(2.2)/ 33.9 | -14.2(0.9)/19.4 |
| | **35.0 (4.1)/ 67.8** | **5.0 (2.1)/ 30.6** | **-2.2(1.7)/ 23.4** | **5.7 (3.1)/ 44.2** | **-9.7(1.7)/ 25.8** | **-7.4(2.9)/ 41.0** | **-9.4(1.4)/21.6** |
| 0) | 41.0 (4.3)/ 73.0 | 9.0 (2.2)/ 32.5 | 1.6(1.7)/ 24.2 | 9.9 (3.2)/ 46.6 | -6.0(1.8)/ 25.5 | -5.3(2.9)/ 41.5 | -7.3(1.4)/21.1 |
| | 22.0 (3.6)/ 55.3 | -1.7 (1.9)/ 27.3 | -5.6(1.5)/ 21.5 | 1.8 (2.9)/ 41.2 | -8.6(1.5)/ 23.1 | -11.6(2.5)/ 37.3 | -12.0(1.1)/20.1 |
| | **68.4 (7.3)/123.2** | **34.6 (4.5)/ 72.2** | **3.1(2.5)/ 35.7** | **8.3 (4.7)/ 67.3** | **-9.0(2.2)/ 32.6** | **-9.0(3.6)/ 51.5** | **-13.7(1.9)/30.5** |
| 0) | 83.4 (7.9)/138.7 | 47.1 (4.9)/ 83.4 | 10.7(2.7)/ 39.7 | 16.2 (5.1)/ 73.4 | -2.4(2.4)/ 33.6 | -5.1(3.7)/ 53.0 | -9.8(2.0)/30.0 |
| | 61.9 (7.5)/122.1 | 35.3 (4.4)/ 71.1 | 6.9(2.4)/ 34.8 | 5.0 (4.6)/ 65.7 | 2.5(2.2)/ 31.4 | -6.5(3.3)/ 46.8 | -4.9(1.8)/26.0 |
| | **241.0(15.1)/321.9** | **96.1 (7.4)/142.3** | **28.4(4.8)/ 73.6** | **48.1 (9.1)/136.7** | **-6.5(3.8)/ 53.9** | **-12.8(5.2)/ 73.9** | **-21.5(2.7)/44.3** |
| 5) | 306.6(17.5)/393.5 | 126.6 (8.5)/174.3 | 50.0(5.6)/ 92.9 | 74.3(10.6)/166.4 | 7.7(4.3)/ 61.7 | -5.8(5.6)/ 78.5 | -15.0(3.0)/44.3 |
| | 341.9(22.6)/460.4 | 118.0 (9.0)/173.2 | 52.2(5.4)/ 91.8 | 63.6(10.1)/155.5 | 24.6(4.5)/ 68.1 | 4.5(5.6)/ 78.5 | 4.6(3.1)/44.2 |
| | **508.4(20.4)/584.3** | **288.0(13.6)/346.0** | **104.0(7.4)/147.3** | **143.7(13.4)/237.5** | **-10.9(4.9)/ 70.4** | **-22.3(6.4)/ 93.0** | **-28.5(4.2)/65.0** |
| 25) | 660.1(23.6)/739.4 | 387.6(16.1)/449.3 | 161.0(9.2)/206.7 | 214.6(16.7)/318.3 | 12.5(6.2)/ 87.8 | -10.9(7.3)/103.0 | -17.5(4.7)/69.1 |
| | 543.1(45.5)/594.2 | -(*) | -(*) | 204.7(16.9)/312.5 | 31.7(6.7)/100.1 | 11.0(8.3)/118.0 | 19.6(5.8)/83.8 |

No convergence.

positive value, but in most cases turns negative. This agrees with asymptotic under-estimation for p and m fixed and $q \to \infty$, i.e. with respect to these asymptotics the estimator for heritability is inconsistent. The root mean squared error decreases with decreasing p or increasing q. Note that within a column of the table, the decrease in root mean squared error is getting smaller with increasing number of offspring m. The most effective reduction is obtained with a larger number of sires.

Possibilities for inference on $h^2$, with or without correction, seem to be limited when the number of sires is in the order of 50, even with a relatively small number of fixed effects in the model. Likewise, with less than 40 observations per sire, we cannot estimate $h^2$ with reasonable accuracy. Although the bias in some instances may be acceptable, the root mean squared error is very high. For an animal model this suggests that individuals should at least roughly fall into more than 50 clusters, and preferably into as much as 200, with an average clustersize of more than 40, and strong familial relationships within clusters, i.e. many half sibs. We conjecture that for the first column and the bottom two rows, no useful inference is possible with MAP / PQL / IRREML / MAPHL or any other estimation procedure. Discussion will be restricted to the remaining part of the table. Even then, as a consequence of the large, but realistic, incidence of 0.90, root mean squared errors remain sizeable.

In a number of instances, where the bias is negative, the correction factor alleviates the bias. The reduction in absolute bias for p = 38 or 1 and q = 200 varies from about 25 to 75 %. This implies that for many "ordinary" statistical problems, with a relatively small number of fixed effects and a large number of random effects, the bias correction factor is a useful asset. The factor is derived under the asymptotics: p and m fixed and $q \to \infty$. With a smaller number of random effects, e.g. q = 50, or a larger number of fixed effects, e.g. p = 139, these asymptotics do not always apply. The bias may be positive, in which case it will be increased by the correction factor which is larger than 1. In that case, with the alternative weights, the bias is often reduced. Since a large number of fixed effects is a common feature in animal breeding, the bias correction factor is of little use for animal models. Although for estimates obtained with the alternative weights, the root mean squared error is often smaller than for estimates without correction or after use of the correction factor, neither correction method seems to affect the root mean squared error to any great extent. For q = 50 sires, estimates under the alternative weights often have smaller absolute bias as well. However, for ample offspring per sire, e.g. m = 61, there is a tendency towards a sizeable negative bias, which is clearly an undesirable feature.

## 5 Discussion

Scope for reduction of bias by employing the Breslow and Lin (1995) correction factor for MAP / PQL / IRREML / MAPHL estimates for heritability or intra-class correlation in threshold models for animal breeding data seems slim for large numbers of small families,

because of the large number of fixed effects involved. Use of the alternative iterative weights (3), as suggested in Engel et al. (1995), may alleviate the bias and reduce root mean squared error, but for larger numbers of offspring per sire tends to produce a sizeable negative bias. For applications outside animal breeding, with much smaller numbers of fixed effects, the bias correction factor can be quite successful. Approximation of the (posterior) distribution of the random effects conditional upon the observations, which is at the root of the problem (for p and m fixed and $q \rightarrow \infty$ approximation by Laplace integration breaks down), can be circumvented by use of Markov chain Monte Carlo (MCMC) techniques, such as Gibbs sampling, see e.g. Zeger and Karim (1991) and Karim and Zeger (1992). That is, if one is prepared to use (some) Bayesian concepts. Simulation results in Zeger and Karim (1991) (for data far from representative for animal breeding), suggest that posterior means for variance components, obtained with Gibbs sampling, are positively biased by 20 - 30%. For the binary salamander mating data (McCullagh and Nelder, 1989, §14.5) analysed with Gibbs sampling in Karim and Zeger (1992), the medians of the posterior distributions of the components of variance are much larger than the MAP / PQL / IRREML / MAPHL estimates (Drum and McCullagh, 1993). Computational demands of Gibbs sampling are high. Problems with respect to choice of length of the Gibbs chain, convergence (which can be very slow for animal models due to the correlation between the random effects) and the use of non-informative priors are summarized in Zeger and Karim (1991). McCulloch (1994) applies a combination of the EM algorithm and Gibbs sampling to the salamander mating data to derive (non-Bayesian) maximum likelihood estimates. Finally, MAP / PQL / IRREML / MAPHL have quasi-likelihood features in the sense that estimation can be formulated in terms of first and second moments only. IRREML, for instance, in Engel and Keen (1994) is motivated by iterative use of MINQUE, which can be re-formulated as iterative use of least squares on squares and products of error contrasts (i.e. contrasts with zero expectation). An important point is to what extent any reduction of bias and/or root mean squared error with MCMC techniques is at cost of lack of robustness with respect to distributional assumptions.

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# Chapter 9

## Prediction of breeding values with a mixed model with heterogeneous variances for large scale dairy data

Submitted for publication.

IRREML applied to a multiplicative mixed model for normal data with heterogeneous variances.

# Prediction of breeding values with a mixed model with heterogeneous variances for large scale dairy data

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**Summary** Evaluation of Dutch dairy data showed serious discrepancies between breeding values based on progeny records and expected values based on parent averages. Apparent heterogeneity of variances between herds offered a possible explanation for these differences. This paper describes the development of a national breeding evaluation method for Dutch dairy cattle that accounts for variance heterogeneity. With the new method the mean difference between estimated breeding values and parent averages was reduced by 38 % compared with evaluation under the traditional assumption of homogeneous variances. The improved method is computationally feasible for the large scale data sets which are commonly used in the dairy industry. Problems with application to Dutch milk yield data, comprising 12,629,403 records, are discussed.

***Keywords:*** BLUP, multiplicative mixed model, variance heterogeneity, Laplace integration

## 1. Introduction

In many countries, breeding values for dairy cattle are estimated employing a mixed analysis of variance model, referred to as an 'animal model' (see e.g. Henderson, 1984, Ch.22). In this model, breeding values, which express the genetic potential of individuals for milk production, are represented by random effects. Due to selection of the best animals for mating, animals may be strongly related to each other. The animal model includes correlations between the random genetic effects due to familial relationships. When all animals involved in selection over the years are present in the data, non-random sampling will be accounted for by these correlations (Henderson, 1984, Ch.13). Also, when records of relatives are included, improved estimates for breeding values will be obtained. Therefore, data sets employed for evaluation of breeding values are commonly extremely large. Animals are selected on the basis of best linear unbiased predictions (BLUPs) (Searle, Casella and McCulloch, 1992, Ch.7; Robinson, 1991) of their breeding values. BLUPs have attractive properties for selection purposes (see e.g. Searle et al., 1992, Ch.7 for references).

Data on 305-day milk yield from Dutch dairy cows as analysed by Van der Werf, Meuwissen and De Jong (1994) showed serious discrepancies between predicted breeding values (expressed in kilograms milk) and values expected on the basis of parent averages. For black and white bulls for instance, estimated breeding values were on average 157 kg lower than expected on the basis of parent means. One of the assumptions underlying the animal model is homogeneity of variances. Heterogeneity of variances in combination with selection of the best animals for mating may explain at least part of the discrepancies found. For instance, when bull dams with a high production are selected for mating they will tend to be selected from the more variable herds. Test daughters of the bulls are tested on average herds. Consequently, evaluations of the bulls will tend to be lower than expected on the basis of their parent averages. Heterogeneity of within herd variances was found in a number of studies (for references see Meuwissen, De Jong and Engel, 1996), and was apparent in the study of Van der Werf et al. (1994) as well. Not in the least because of large financial interests involved it was paramount to account for this heterogeneity in the Dutch breeding value evaluation system.

This paper describes the development and implementation of the new evaluation system and its application to Dutch milk yield data. The new system is computationally feasible for large data sets. Data analysed in this paper comprised 12,629,403 milk yield records and is summarized in Section 2. The model is discussed in Section 3. Both means and variances are expressed in terms of fixed and random effects, involving both additive and, through the use of scaling factors, multiplicative effects. A similar model was proposed by Kachman and Everett (1993), but with a different choice of (prior) distribution of the random effects, and different, computationally challenging, estimating equations. In contrast to Foulley, San Cristobal, Gianola and Im (1992), heterogeneity in the model is not restricted to the residual (environmental) variance, but applies to the genetic variance as well. Predicted breeding values based on scaled records are derived in Section 4. Problems encountered in the application to the Dutch dairy data are discussed in Section 5. Simulation results are presented in Section 6. In Section 7, employing the Laplace approximation for the likelihood, estimating equations are shown to be approximations of the maximum likelihood equations.

## 2. The Dutch milk yield data

Milk production data was obtained from the Dutch Cattle Syndicate (NRS) from cows freshening in The Netherlands between July 1978 and December 1994. Data was collected from first to third lactation, if available, and comprised 12,629,403 records from 5,819,606 cows in 42,480 herds. The number of herd-year combinations was 499,608. The number of years per herd varied from 1 to 17, with an average of 11.8. For almost half of the herds the number of years was 15 or more. Some summary statistics are shown in Table 1.

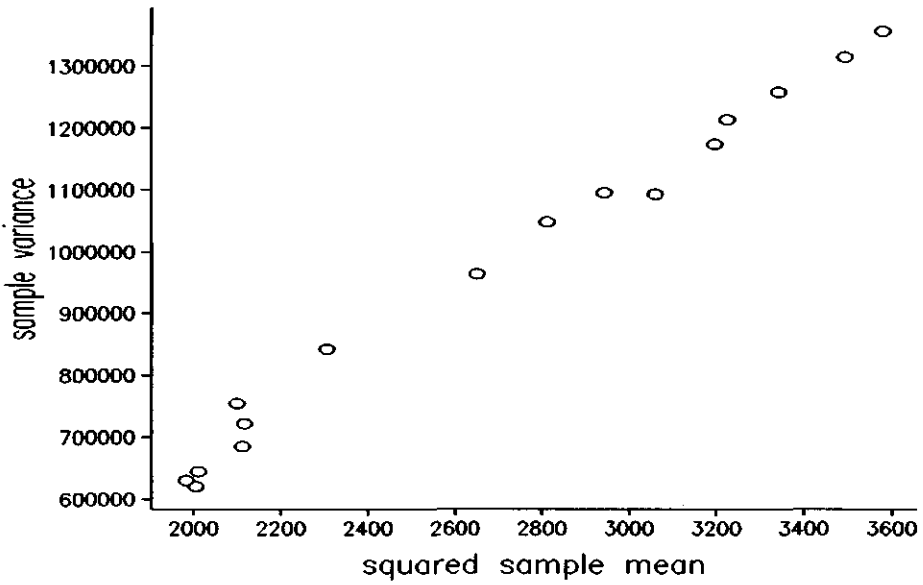
**Table 1.** Summary statistics of the Dutch dairy data. Percentile points and means for average production, standard error for production and number of lactations (cows) per herd, per year[1].

| | 10% | mean | 90% |
|---|---|---|---|
| per herd, per year: | | | |
| average production (kg) | 3946 | 5027 | 6276 |
| standard deviation for production (kg) | 456 | 693 | 947 |
| number of cows | 5 | 25.3 | 47 |

[1] A year is from October to next September.

In Figure 1, sample variances are plotted against squared sample means for the years. Squared means were chosen for later use in Section 5. Clearly, the variance increases with the mean.

**Figure 1.** Sample variances plotted against squared sample means ($* 10^{-4}$) for each of the years in the Dutch dairy data.



## 3. The model

For the i-th herd-year (HY) class, i = 1...p, the vector $\mathbf{y}_i$ of milk yield data is modelled by:

$$\mathbf{y}_i = (\mathbf{X}_i\mathbf{b} + \mathbf{Z}_i\mathbf{u} + \mathbf{e}_i)\,\phi_i, \tag{1a}$$

where $\mathbf{b}$, $\mathbf{u}$ and $\mathbf{e}_i$ are vectors of fixed effects, genetic effects (breeding values) and residual (environmental) effects respectively, $\mathbf{X}_i$ and $\mathbf{Z}_i$ are design matrices, and $\phi_i$ is a scaling factor. Fixed effects in $\mathbf{b}$ include effects for differences between herds, years and seasons. Scaling factors allow for variance heterogeneity between HY classes. Furthermore:

$$\mathbf{u} \sim N(\mathbf{0},\, \mathbf{A}\sigma_a^2) \quad \text{and} \quad \mathbf{e}_i \sim N(\mathbf{0},\, \mathbf{I}_i\sigma_e^2). \tag{1b}$$

Variance components $\sigma_a^2$ and $\sigma_e^2$ represent variation due to genetic and environmental effects, respectively. Matrix $\mathbf{A}$, the additive relationship matrix, accounts for correlations between genetic effects of relatives. For instance, covariance between halfsibs, e.g. cows with the same sire but different dams, is $¼\sigma_a^2$ and ¼ will be entered in the appropriate position in matrix $\mathbf{A}$. $\mathbf{I}_i$ are identity matrices of appropriate sizes.

An important concept in animal breeding is heritability, which is the amount of variance 'explained' by genetic effects relative to the total variance. Here, heritability is assumed to be the same across HY classes:

$$h^2 = \sigma_a^2 / (\sigma_a^2+\sigma_e^2).$$

Without loss of generality $\sigma_e^2$ may be fixed at value 1. In evaluation of breeding values, $h^2$ is usually assumed to be known. The value for $h^2$ is based on analyses of previous data sets (typically much smaller than those used for evaluation of breeding values). In principle, there is no problem in providing an estimating equation for $h^2$ as well, but we will not do so and assume $h^2$ and consequently $\sigma_a^2$ to be known.

Heterogeneity factors are assumed to follow a log linear model:

$$\log(\phi_i^2) = \mathbf{t}_i'\boldsymbol{\theta}, \tag{1c}$$

where $\boldsymbol{\theta}$ is a vector of dispersion parameters, including a constant, and $\mathbf{t}_i$ is a design vector. Initially, $\boldsymbol{\theta}$ will be assumed to consist of fixed effects only and maximum likelihood (ML) equations will be derived in Section 4.1. Since the number of HY classes will be large, with a modest number of observations per HY class, it is profitable to introduce random effects in $\boldsymbol{\theta}$. Since heterogeneity factors for successive years are expected to be similar, in Section 4.2. the analysis will be extended towards a first order autoregressive correlation structure for years within herds.

## 4. Estimation of parameters and prediction of breeding values

### 4.1 Estimation and prediction for non-random scale factors

The 'complete' log likelihood $L_c$ is taken to be (the kernel) of the logarithm of the joint pdf of **y** and **u**:

$$L_c = -\ ½\ \Sigma\ n_i\ \log(\phi_i^2) - ½\ \Sigma\ \mathbf{e}_i'\mathbf{e}_i - \ ½\ \mathbf{u}'\mathbf{A}^{-1}\mathbf{u}\ /\ \sigma_a^2,$$

where $n_i$ is the number of records in the i-th HY class. Derivatives with respect to **b** and **u**, when set equal to **0**, yield what is commonly referred to as the mixed model equations (Searle et al., 1992, Ch. 12), expressed in terms of scaled records $\mathbf{y}_* = (\mathbf{y}_{*1}'...\mathbf{y}_{*p}')' = (\mathbf{y}_1'/\phi_1...\mathbf{y}_p'/\phi_p)'$:

$$\begin{pmatrix} \mathbf{X}'\mathbf{X} & \mathbf{X}'\mathbf{Z} \\ \mathbf{Z}'\mathbf{X} & \mathbf{Z}'\mathbf{Z} + \sigma_a^{-2}\mathbf{A}^{-1} \end{pmatrix} \begin{pmatrix} \hat{\mathbf{b}} \\ \hat{\mathbf{u}} \end{pmatrix} = \begin{pmatrix} \mathbf{X}'\mathbf{y}_* \\ \mathbf{Z}'\mathbf{y}_* \end{pmatrix} . \qquad (2)$$

ML equations for **b** are of the form $E[\partial L_c / \partial \mathbf{b}) \mid \mathbf{y}] = \mathbf{0}$ (Louis, 1982). Since (2) is linear in **u**, it follows that solutions $\hat{\mathbf{b}}$ and $\hat{\mathbf{u}}$ are ML estimates of **b** and predictions $E(\mathbf{u} \mid \mathbf{y})$ (evaluated for $\hat{\mathbf{b}}$) of **u**, respectively. Matrix **A** is very large and can be inverted with techniques developed by Henderson (1976) and Quaas (1976). ML equations $E[(\partial L_c / \partial \theta) \mid \mathbf{y}] = \mathbf{0}$ for $\theta$ are:

$$\Sigma \mathbf{t}_i \hat{z}_i = \mathbf{0}, \quad \text{where} \quad \hat{z}_i = (\mathbf{y}_{*i}'\hat{\mathbf{e}}_i - n_i) / 2 \quad \text{and} \quad \hat{\mathbf{e}}_i = \mathbf{y}_{*i} - \mathbf{X}_i\hat{\mathbf{b}} - \mathbf{Z}_i\hat{\mathbf{u}}. \qquad (3)$$

Considering $z_i = (\mathbf{y}_{*i}'\mathbf{e}_i - n_i) / 2$, i = 1...p, as estimating functions for $\theta$, combination into one equation (see e.g. McCullagh and Nelder, 1989, §9.4.2), conditional upon **u**, also leads to (3). Because $z_i = (\partial L_c/\partial \eta_i)$ is a score function, where $\eta_i = \log(\phi_i^2)$: $\mathrm{Var}(z_i \mid \mathbf{u}) = E[(\partial L_c/\partial \eta_i)^2 \mid \mathbf{u}] = -E[(\partial^2 L_c/\partial \eta_i^2) \mid \mathbf{u}] = -E[\partial z_i/\partial \eta_i \mid \mathbf{u}] = \{2n_i + (\mathbf{X}_i\mathbf{b}+\mathbf{Z}_i\mathbf{u})'(\mathbf{X}_i\mathbf{b}+\mathbf{Z}_i\mathbf{u})\} / 4 = w_i$, say. Expansion of $\mathbf{z} = (z_1...z_p)'$ around initial estimates $\hat{\theta}$ yields: $\mathbf{z} \approx \hat{\mathbf{z}} - \hat{\mathbf{W}}\mathbf{T}(\theta - \hat{\theta})$ or $\hat{\mathbf{W}}^{-1}\hat{\mathbf{z}} + \mathbf{T}\hat{\theta} \approx \hat{\mathbf{W}}^{-1}\mathbf{z} + \mathbf{T}\theta$, where $\hat{\mathbf{W}} = \mathrm{diag}(\hat{w}_i)$ and $\mathbf{T} = (\mathbf{t}_1...\mathbf{t}_p)'$. Hence, the following vector $\zeta$ of "pseudo-observations", approximately follows a linear model:

$$\zeta = \hat{\mathbf{W}}^{-1}\hat{\mathbf{z}} + \mathbf{T}\hat{\theta}, \quad \text{with} \quad E(\zeta \mid \mathbf{u}) \approx \mathbf{T}\theta \quad \text{and} \quad \mathrm{Var}(\zeta \mid \mathbf{u}) \approx \hat{\mathbf{W}}^{-1}. \qquad (4)$$

Employing (4), equations (3) may be solved with repeated use of weighted regression on $\zeta$. After each regression step, $\zeta$ and $w_i$ are updated, employing current estimates and predictions. This is equivalent to Fisher scoring. An obvious approach is to alternate between solving (2), for current values of $\phi_i$, and solving (3), for current values of **b** and **u**. This is similar to the see-saw algorithm for extended quasi-likelihood suggested in McCullagh and Nelder (1989, §10.2).

### 4.2. Estimation and prediction for random scale factors

Let $\boldsymbol{\theta}$ consist of fixed effects $\boldsymbol{\beta}$ and random effects $\boldsymbol{\delta}$, with design matrices **B** and **D** respectively:

$$2\log(\boldsymbol{\phi}) = \mathbf{B}\boldsymbol{\beta} + \mathbf{D}\boldsymbol{\delta}, \quad \text{where} \quad \boldsymbol{\phi} = (\phi_1 \ldots \phi_p)' \quad \text{and} \quad \boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2 \mathbf{R}).$$

The auto-correlation matrix **R** depends on the unknown correlation $\rho$ between random effects $\delta$ in successive years within herds. Equations (2) will be retained, employing predicted scaling factors. Equations (3) will be modified and additional equations for $\sigma_\delta^2$ and $\rho$ will be derived. Moments in (4) are still valid, but conditional upon $\boldsymbol{\delta}$ as well, with $\mathbf{T} = (\mathbf{B}, \mathbf{D})$ and $\boldsymbol{\theta} = (\boldsymbol{\beta}', \boldsymbol{\delta}')'$. Marginally with respect to $\boldsymbol{\delta}$, $\boldsymbol{\zeta}$ approximately follows a linear mixed model, with fixed effects $\boldsymbol{\beta}$, random effects $\boldsymbol{\delta}$, "residual variance" equal to 1 and "residual weights" $\hat{w}_i$. Weighted regression is replaced by weighted restricted maximum likelihood (REML; Patterson and Thompson, 1971), similarly to modification of iterative re-weighted least squares in generalized linear mixed models (e.g. Schall, 1991; Engel and Keen, 1994; Engel, Buist and Visscher, 1995; Engel and Buist, 1996). Mixed model equations for $\boldsymbol{\theta}$, in terms of $\boldsymbol{\zeta}$, are:

$$(\mathbf{T}'\hat{\mathbf{W}}\mathbf{T} + \text{diag}(\mathbf{0}, \mathbf{R}^{-1}\sigma_\delta^{-2}))\hat{\boldsymbol{\theta}} = \mathbf{T}'\hat{\mathbf{W}}\boldsymbol{\zeta}. \tag{5a}$$

Substitution of $\boldsymbol{\zeta}$ from (4) shows that at convergence the following equations are solved:

$$\Sigma \mathbf{T}_i \hat{z}_i = \text{diag}(\mathbf{0}, \sigma_\delta^{-2} \mathbf{R}^{-1}\hat{\boldsymbol{\delta}}). \tag{5b}$$

$L_c$ now includes the quadratic $-\frac{1}{2}\,\boldsymbol{\delta}'\mathbf{R}^{-1}\boldsymbol{\delta}\,\sigma_\delta^{-2}$ and derivatives of $L_c$ with respect to $\boldsymbol{\beta}$ and $\boldsymbol{\delta}$, when set to 0, also yield (5b). With respect to the fixed effects model for the scaling factors in Section 4.1., $\sigma_\delta^2$ and $\rho$ may also be considered as smoothing parameters for the estimated heterogeneity factors, employing a quadratic penalty function. Each iteration $\sigma_\delta^2$ is updated by:

$$\hat{\sigma}_\delta^2 = \{\hat{\boldsymbol{\delta}}'\mathbf{R}^{-1}\hat{\boldsymbol{\delta}} + \text{trace}(\mathbf{R}^{-1}\mathbf{C})\} \;/\; q. \tag{6}$$

Here, **C** is the part of the inverse of the coefficient matrix of (5a) corresponding to the q elements of $\boldsymbol{\delta}$, and the right-hand-side is evaluated for current parameter values and predictions. This is an approximate ML equation, as will be shown in Section 6. Similarly, $\rho$ is updated by:

$$\hat{\rho} = \sum_j \{\sum_k \hat{\delta}_{k\,j-1}\hat{\delta}_{k\,j} + \text{trace}(\mathbf{C}_{j-1\;j})\} \;/\; \{\hat{\sigma}_\delta^2 \,\Sigma\, q_{j-1\;j}\}. \tag{7}$$

Here, $\hat{\delta}_{kj}$ is the element of $\hat{\boldsymbol{\delta}}$ for the j-th year and k-th herd, $\mathbf{C}_{j-1\;j}$ is a submatrix of **C**,

restricted to the $q_{j-1\,j}$ herds common to the subsequent years j-1 and j. Note that (6) and (7) are approximate moment estimators. E.g. in expression (6), $\hat{\boldsymbol{\delta}}'\mathbf{R}^{-1}\hat{\boldsymbol{\delta}} = \boldsymbol{\delta}'\mathbf{R}^{-1}\boldsymbol{\delta} - (\hat{\boldsymbol{\delta}}-\boldsymbol{\delta})'\mathbf{R}^{-1}(\hat{\boldsymbol{\delta}}-\boldsymbol{\delta}) + 2(\hat{\boldsymbol{\delta}}-\boldsymbol{\delta})'\mathbf{R}^{-1}\hat{\boldsymbol{\delta}}$, with expected values $q\sigma_\delta^2$, -trace($\mathbf{R}^{-1}\mathbf{C}$) and 0 for terms on the right-hand-side, if $\hat{\delta}$ is evaluated for the true parameter values under the approximate linear mixed model for $\zeta$.

In the application to the Dutch dairy data, constant $\beta$ is the only fixed effect for the scaling factors, $\mathbf{B} = \mathbf{1}$ is a vector with all elements equal to 1 and $\mathbf{D}$ is an identity matrix. Equations (5a) can be rewritten as:

$$(\mathbf{W} + \mathbf{R}^{-1}\sigma_\delta^{-2})\hat{\boldsymbol{\delta}} = \mathbf{W}(\boldsymbol{\zeta} - \hat{\beta}\mathbf{1}), \tag{8a}$$

$$\hat{\beta} = \Sigma\, w_i(\zeta_i - \delta_i) \,/\, \Sigma w_i. \tag{8b}$$

Equations (8a) can be solved for $\boldsymbol{\delta}$, evaluating the coefficient matrix and the right-hand-side for current estimates and predictions, and then $\beta$ can be updated from (8b), using the new values for $\boldsymbol{\delta}$. Since (8a,b) are only part of the total iteration process, it suffices to do this once or a few times only. Data can be ordered as years within herds and read one herd at a time, taking advantage (Press, Teukolsky, Vetterling and Flannery, 1992, §2.4) of the tridiagonal structure of $\mathbf{R}^{-1}$ (see Wade, Quaas and Van Vleck, 1993). Note that trace($\mathbf{R}^{-1}\mathbf{C}$) in (6) equals:

$$\Sigma\,\mathrm{trace}(\mathbf{R}_k^{-1}(\mathbf{W}_k+\mathbf{R}_k^{-1}\hat{\sigma}_\delta^{-2})^{-1})+\{\Sigma\omega_k'(\mathbf{W}_k+\mathbf{R}_k^{-1}\hat{\sigma}_\delta^{-2})^{-1}\mathbf{R}_k^{-1}(\mathbf{W}_k+\mathbf{R}_k^{-1}\hat{\sigma}_\delta^{-2})^{-1}\omega_k\}/\{\Sigma\Sigma w_{kj}-\Sigma\omega_k'(\mathbf{W}_k+\mathbf{R}_k^{-1}\sigma_\delta^{-2})^{-1}\omega_k\},$$

where vector $\omega_k$ and diagonal matrix $\mathbf{W}_k$ contain the weights for herd k. $\mathbf{R}$ is blockdiagonal with block $\mathbf{R}_k$ for herd k. Thus trace($\mathbf{R}^{-1}\mathbf{C}$) can be evaluated reading the data one herd at a time.

## 5 Application to the Dutch milk yield data

In the model fitted to the Dutch milk yield data, fixed effects were included for combinations of parity, herd, year and season of calving, for combinations of month and year of calving and for genetic groups. For the use of fixed genetic group effects see Quaas (1988). In addition to additive genetic animal effects the model included permanent environmental effects. The latter effects account for correlation between environmental effects for observations on the same animal. Inclusion of these random effects in (1a) is straightforward. Heritability was taken to be 0.35. Permanent environmental variance relative to the total variance was set to 0.20, i.e. correlation between observations on the same animal was 0.35 + 0.20 = 0.55. A diagonal matrix of residual prior weights related to preadjustment of the data as described by Van der Werf et al. (1994) was included as well.

Sofar, for the mean $\bar{y}$ of a random herd within a year, $E(\bar{y} \mid \phi) = \alpha\phi$ and $Var(\bar{y} \mid \phi) = \gamma\phi^2$,

say. Marginally, under some regularity conditions on $\alpha$ and $\gamma$, $E(\bar{y}) = E(\alpha)\,E(\phi) = m$, say, and $Var(\bar{y}) = \{E(\gamma)+Var(\alpha)\}\ E(\phi^2) + E(\alpha)^2\ Var(\phi)$. From properties of the lognormal distribution it follows that $Var(\bar{y})$ is a linear function of $m^2$. The relationship between sample variances and squared means for the years is indeed fairly linear, as can be seen in Figure 1.

The iteration process showed a tendency for $\rho$ to exceed value 1. Although unexpected, $\rho = 1$ may be realistic, simply indicating that the more simple model with only random herd effects for the heterogeneity factors would be sufficient. A trend over the years in the log linear model for the scale factors was considered, but inclusion of fixed year effects just slowed the iteration process down, without improvement. A numerically more robust version of (6) and (7) was implemented. Separate updates for variances and covariances for the J different years and pairs of consecutive years were calculated and combined afterwards:

$$\sigma^2_{\delta\,j} = \{\hat{\boldsymbol{\delta}}_j'\hat{\boldsymbol{\delta}}_j + \text{trace}(\mathbf{C}_{jj})\} \,/\, q_j,\quad \sigma_{\delta\,j-1\,j} = \{\Sigma\ \hat{\delta}_{k\,j-1}\hat{\delta}_{kj} + \text{trace}(\mathbf{C}_{j-1\,j})\} \,/\, q_{j-1\,j},$$
$$\hat{\sigma}^2_{\delta} = \Sigma\ \sigma^2_{\delta\,j} \,/\, J \quad \text{and} \quad \hat{\rho} = \Sigma\ \{\sigma_{\delta\,j-1\,j} \,/\, (\sigma_{\delta\,j-1}\sigma_{\delta\,j-1})\} \,/\, (J-1) = \Sigma\ \hat{\rho}_j \,/\, (J-1). \tag{9}$$

Here, $q_j$ is the number of herds involved in subvector $\hat{\boldsymbol{\delta}}_j$ of $\boldsymbol{\delta}$ and $\mathbf{C}_{jj}$ is a submatrix of $\mathbf{C}$, for year j. A stable procedure to solve the estimating equations was found to be the following (where [t] denotes the current iteration number):

1. Update breeding values from (2), performing one iteration cycle with an efficient method proposed by Schaeffer and Kennedy (1986);
2. If $Q = (\hat{\mathbf{u}}_{[t]}-\hat{\mathbf{u}}_{[t-1]})'(\hat{\mathbf{u}}_{[t]}-\hat{\mathbf{u}}_{[t-1]}) \,/\, \hat{\mathbf{u}}_{[t]}'\hat{\mathbf{u}}_{[t]} < 10^{-8}$ solve $\beta$ from (8b), else solve (8a) as well. Go back to 1, unless $Q < 10^{-8}$ for 5 iterations in a row;
3. Solve $\hat{\sigma}^2_{\delta[t]}$ from (9). If $\{(\hat{\sigma}^2_{\delta[t]}-\hat{\sigma}^2_{\delta[t-1]})^2 \,/\, \hat{\sigma}^4_{\delta[t]}\} > 10^{-10}$ go back to 1;
4. Solve $\hat{\rho}_{[t]}$ from (9). If $\{(\hat{\rho}_{[t]}-\hat{\rho}_{[t-1]})^2 \,/\, \hat{\rho}^2_{[t]}\} > 10^{-10}$ go back to 1, else stop.

Results for the Dutch milk yield data are shown in Table 2. Although the separate updates from the last iteration show a slight dip around 1986, all are close to their respective averages $\hat{\rho} = 0.984$ and $\hat{\sigma}^2_{\delta} = 0.10$.

The coefficient of variation for the heterogeneous variances is $\sqrt{\{\exp(\hat{\sigma}^2_{\delta})-1\}} = 0.33$, which is close to the estimated value 0.31 of Van der Werf et al. (1994). $\hat{\rho} = 0.984$ is near enough to 1 to suggest that under the present circumstances the simpler model with only random herd effects for the heterogeneity factors would be adequate. The new evaluation method had to be operational on short notice early 1995 and it was decided to implement (9). A decision, on the basis of simulation results obtained afterwards, we did not have to regret.

**Table 2.** $\sigma^2_{\delta j}$, $\hat{\rho}_j$, $\hat{\sigma}^2_\delta$ and $\hat{\rho}$ from (9) for the Dutch dairy data.

| year j' | $\hat{\rho}_j$ | $\hat{\sigma}^2_{\delta j}$ |
|---|---|---|
| 1978 | 0.992 | 0.107 |
| 1979 | 0.991 | 0.108 |
| 1980 | 0.990 | 0.108 |
| 1981 | 0.988 | 0.105 |
| 1982 | 0.984 | 0.102 |
| 1983 | 0.977 | 0.100 |
| 1984 | 0.974 | 0.095 |
| 1985 | 0.967 | 0.092 |
| 1986 | 0.970 | 0.091 |
| 1987 | 0.976 | 0.092 |
| 1988 | 0.982 | 0.093 |
| 1989 | 0.985 | 0.099 |
| 1990 | 0.991 | 0.104 |
| 1991 | 0.992 | 0.110 |
| 1992 | 0.994 | 0.114 |
| 1993 | - | 0.114 |
| average | 0.984 | 0.102 |

' A year is from October to next September, e.g. j = 1978 denotes October 1978 to September 1979.

Some results for estimated breeding values are summarized in Table 3. Differences between estimated breeding values (EBV) and parent averages (PA) are reduced by 38 % ( = (1-78/126) * 100 %) when heterogeneity is taken into account. The prediction error variance (not shown) decreased by 18 %. EBVs and PAs were obtained from the same run of the model. Therefore, differences can be expected to be somewhat smaller than when PA's are derived from an earlier analysis. The average reduction in EBV - PA for $\rho = 0.50$ of 35 % suggests that the value for $\rho$ is not too critical.

## 6 Simulation results

Records were generated according to (1a, b, c). The model for analysis included herd-year effects in **b**. These effects were not included in the data generation, i.e. their true values were 0 . Individuals were unrelated, i.e. **A** was an identity matrix.

**Table 3.** Estimated breeding values (EBV) minus parent averages (PA') Differences in kg milk for 1520 progeny tested Black and White bulls born between 1981 and 1990 without heterogeneity correction and for $\rho$ = 0, 0.50, 0.75, 0.984 and $\sigma^2_\delta$ = 0.10.

| | | |
|---|---|---|
| EBV-PA, no correction | | -126 (kg) |
| EBV-PA, $\rho$ = 0 | | -113 |
| EBV-PA, $\rho$ = 0.50 | | - 81 |
| EBV-PA, $\rho$ = 0.75 | | - 78 |
| EBV-PA, $\rho$ = 0.984 | | - 78 |
| (EBV without correction) - (EBV for $\rho$ = 0.984) | for sires of bulls | - 41 |
| | for dams of bulls | - 57 |

' PA = $(EBV_{sire} + EBV_{dam}) / 2$. EBV and PA are from the same analysis. Their average difference should be close to 0.

Heterogeneity factors $\phi$ were generated with constant $\beta = 0$. The two schemes employing (6) and (7) or (9) were studied.

Initially we intended to update $\rho$ by regression, but since convergence for the dairy data proved to be problematic, this approach was abandoned. It was however included in the simulation. Our first idea was to update $\rho$ by regression of $\zeta_{kj}$ on $\zeta_{k\,j-1}$ for herd k and subsequent years j-1 and j. The estimating functions approach (see e.g. McCullagh and Nelder, 1989, §9.4) yielded the estimating equation: $\Sigma\,\Sigma\, h_{kj}\, \alpha_{kj}\, (\zeta_{k\,j-1}-\beta) / \nu_{kj} = 0$, where $h_{kj} = (\zeta_{kj}-\beta) - \rho\, \alpha_{kj}\, (\zeta_{k\,j-1}-\beta)$, $\alpha_{kj} = \{\sigma^2_\delta / (\sigma^2_\delta + w^{-1}_{kj-1})\}$, $\nu_{kj} = \sigma^2_\delta + w^{-1}_{kj} - \rho^2\sigma^2_\delta\alpha_{kj}$ and weights $w_i$ are renumbered as $w_{kj}$ for herd k and year j. An update which follows directly from this equation, is:

$$\hat{\rho} = \{\Sigma\,\Sigma\, \alpha_{kj}\, (\zeta_{k\,j-1}-\beta)\, (\zeta_{kj}-\beta)\, \nu^{-1}_{kj}\} / \{\Sigma\,\Sigma\, \alpha^2_{kj}\, (\zeta_{k\,j-1}-\beta)^2\, \nu^{-1}_{kj}\}. \qquad (10)$$

Some results for $\rho$ and $\sigma^2_\delta$ are shown in Table 4a. For regression scheme (6) and (10) estimates of $\rho$ (and of $\sigma^2_\delta$ as well) oscillated strongly before settling down after a very large number of iterations, as shown in Figure 2. This can be avoided by halving the steplength for $\rho$ from one iteration to the next, i.e. $\hat{\rho}_{[t]} = (\hat{\rho}_{[t-1]} + \hat{\rho}) / 2$, where $\hat{\rho}$ is solved from (10). Results in Table 4a are satisfactory for a wide range of values for $\rho$, including values close to 1. In Table 4b results are presented for $\sigma^2_\delta = 0.1$, which is more in line with the Dutch dairy data. The regression estimators, especially for n = 10 animals per HY class, are severely biased. The other two schemes perform well enough with virtually identical results. They differ however with respect to the number of iterations required to satisfy the convergence criteria.

**Figure 2.** The iteration proces for the regression scheme. Iterates $\hat{\rho}_{[t]}$ for $\rho$ are plotted against the iteration number [t]. $\rho = 0.93$, $\sigma_\delta^2 = 1$ and the number of animals per herd is 10. The dotted line corresponds to the original scheme, the drawn line is the result after halving the steplength.

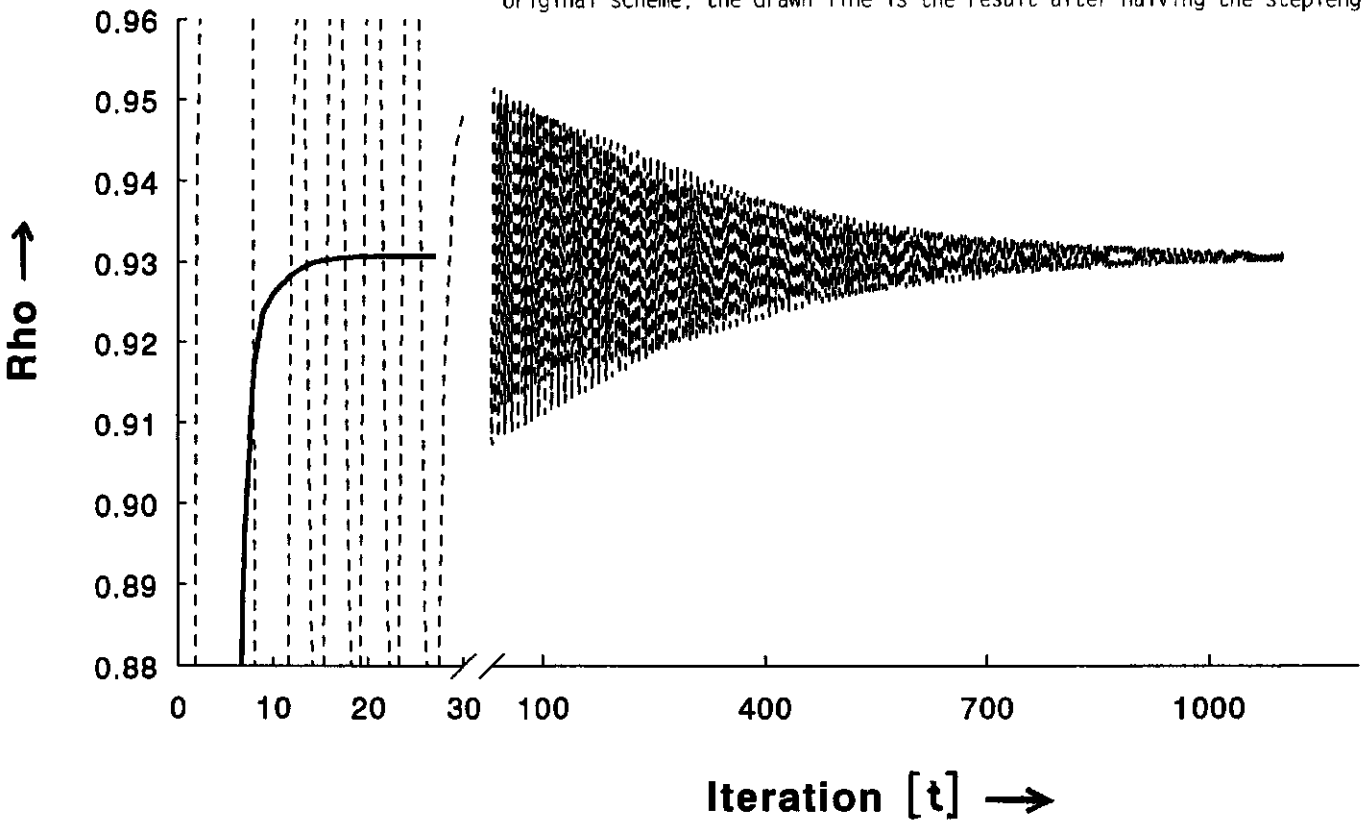


**Table 4a.** Some simulation results for $\rho$ and $\sigma_s^2$ for 1000 herds, 10 years per herd, $\sigma_s^2 = 1$, $\rho$ from 0.95 to 0.05 and $h^2 = 0.30$.

| true value | regr. approach and (7) and (9) | | robust approach (10) | | expressions (7) and (8) | |
|---|---|---|---|---|---|---|
| $\rho$ | $\hat{\rho}$ | $\sigma_s^2$ | $\hat{\rho}$ | $\sigma_s^2$ | $\rho$ | $\sigma_s^2$ |
| 100 animals per herd per year | | | | | | |
| 0.95 | 0.948 | 0.983 | 0.950 | 1.006 | 0.950 | 1.005 |
| 0.90 | 0.899 | 1.009 | 0.898 | 0.998 | 0.898 | 0.999 |
| 0.75 | 0.751 | 1.009 | 0.746 | 0.993 | 0.747 | 0.997 |
| 0.50 | 0.511 | 0.998 | 0.511 | 0.997 | 0.512 | 0.999 |
| 0.25 | 0.251 | 1.011 | 0.251 | 1.011 | 0.252 | 1.012 |
| 0.10 | 0.121 | 1.006 | 0.121 | 1.006 | 0.122 | 1.007 |
| 0.05 | 0.045 | 0.992 | 0.045 | 0.992 | 0.045 | 0.992 |
| 10 animals per herd per year | | | | | | |
| 0.95 | 0.946 | 0.967 | 0.938 | 0.947 | 0.943 | 0.961 |
| 0.90 | 0.914 | 1.034 | 0.906 | 1.013 | 0.915 | 1.041 |
| 0.75 | 0.757 | 0.971 | 0.750 | 0.960 | 0.762 | 0.983 |
| 0.50 | 0.498 | 0.993 | 0.502 | 0.995 | 0.522 | 1.017 |
| 0.25 | 0.254 | 1.024 | 0.253 | 1.024 | 0.282 | 1.050 |
| 0.10 | 0.094 | 1.017 | 0.094 | 1.017 | 0.136 | 1.049 |
| 0.05 | 0.036 | 0.983 | 0.037 | 0.983 | 0.076 | 1.009 |

**Table 4b.** Some simulation results for $\rho$ and $\sigma_s^2$ for 1000 herds, 10 years per herd, $\sigma_s^2 = 0.1$, $\rho$ from 0.95 to 0.05 and $h^2 = 0.30$.

| true value | regr. approach and (7) and (9) | | robust approach (10) | | expressions (7) and (8) | |
|---|---|---|---|---|---|---|
| $\rho$ | $\hat{\rho}$ | $\sigma_s^2$ | $\hat{\rho}$ | $\sigma_s^2$ | $\rho$ | $\sigma_s^2$ |
| 100 animals per herd per year | | | | | | |
| 0.95 | 0.887 | 0.181 | 0.959 | 0.102 | 0.959 | 0.102 |
| 0.90 | 0.849 | 0.156 | 0.897 | 0.097 | 0.898 | 0.097 |
| 0.75 | 0.737 | 0.131 | 0.767 | 0.103 | 0.768 | 0.104 |
| 0.50 | 0.496 | 0.110 | 0.500 | 0.100 | 0.503 | 0.101 |
| 0.25 | 0.223 | 0.103 | 0.224 | 0.098 | 0.228 | 0.098 |
| 0.10 | 0.090 | 0.103 | 0.091 | 0.099 | 0.092 | 0.099 |
| 0.05 | 0.049 | 0.103 | 0.050 | 0.099 | 0.052 | 0.100 |
| 10 animals per herd per year | | | | | | |
| 0.95 | 0.452 | 0.300 | 0.901 | 0.098 | 0.902 | 0.098 |
| 0.90 | 0.477 | 0.294 | 0.878 | 0.098 | 0.877 | 0.098 |
| 0.75 | 0.432 | 0.296 | 0.750 | 0.099 | 0.752 | 0.099 |
| 0.50 | 0.289 | 0.269 | 0.479 | 0.098 | 0.476 | 0.098 |
| 0.25 | 0.117 | 0.252 | 0.179 | 0.097 | 0.176 | 0.097 |
| 0.10 | 0.046 | 0.243 | 0.071 | 0.096 | 0.076 | 0.096 |
| 0.05 | -0.004 | 0.243 | -0.008 | 0.095 | -0.014 | 0.965 |

Scheme (6) and (7) converges faster for high values of ρ, while (9) is faster for low values of ρ. Results for 500 simulated sets of data are shown in Table 5, confirming the breakdown of the regression scheme. It seems that the regression approach does not properly account for shrinkage in the predictions of the random effects which are used to calculate $\zeta$. This becomes apparent for small $\sigma_\delta^2$ and small n.

**Table 5.** Simulations for $\rho = 0.90$ and $\sigma_\delta^2 = 1$ and 0.1. Average values for $\hat{\rho}$ and $\hat{\sigma}_\delta^2$ from 500 simulations. 0.05 (.) and 0.95 [.] percentile points of the 500 estimates are shown below the averages. Simulations are for a 1000 herds, 10 years per herd and 10 animals per herd per year.

| true value of $\sigma_\delta^2$ | regression approach (7) and (9) | | robust approach equations (10) | | equations (7) and (8) | |
|---|---|---|---|---|---|---|
| | $\hat{\rho}$ | $\hat{\sigma}_\delta^2$ | $\hat{\rho}$ | $\hat{\sigma}_\delta^2$ | $\hat{\rho}$ | $\hat{\sigma}_\delta^2$ |
| 1 | 0.910 | 1.008 | 0.903 | 0.992 | 0.903 | 0.992 |
| | (0.897) | (0.966) | (0.889) | (0.945) | (0.888) | (0.945) |
| | [0.921] | [1.047] | [0.917] | [1.038] | [0.917] | [1.039] |
| 0.1 | 0.486 | 0.309 | 0.897 | 0.099 | 0.897 | 0.099 |
| | (0.455) | (0.295) | (0.859) | (0.098) | (0.860) | (0.098) |
| | [0.517] | [0.322] | [0.930] | [0.100] | [0.931] | [0.101] |

## 7 Discussion

From a Bayesian view point, $\hat{\boldsymbol{\beta}}$ and $\hat{\boldsymbol{\delta}}$ from (5b) are joint posterior modes. Equations (5b), rewritten in terms of $\boldsymbol{\Delta} = \boldsymbol{\theta}_{new} - \boldsymbol{\theta}_{old}$ and $\mathbf{z}$, resemble equations (3.26) in Foulley et al. (1992) under their "normal approximation", with weights from their equation (3.16). Because in our paper heterogeneity applies both to genetic and residual variances, the $z_i$'s are similar but not equal to the corresponding quantities in Foulley et al. (1992). The lognormal distribution for the scale factors, which implies a lognormal distribution for $\phi$, $\phi^2$ and $\phi^{-1}$, is similar to the inverted gamma prior in Kachman and Everett (1993). For the small value of 0.33 for the coefficient of variation, degrees of freedom $\nu$ of the inverted chi-square distribution correspond to $2/\sigma_\delta^2$, after scaling such that $E(\phi^{-2}) = 1$. The first two moments of the lognormal and inverted chi-square distributions are about the same: $E(\phi) = \exp(3\sigma_\delta^2/8) + O(\sigma_\delta^4) = 1 + 3/(4\nu) + O(\nu^{-2})$ and $Var(\phi) = \sigma_\delta^2/4 + O(\sigma_\delta^4) = 1/(2\nu) + O(\nu^{-2})$. The main difference between the two estimation procedures is in the use of the approximate linear mixed model for variate $\zeta$, which simplifies matters considerably and offers an opportunity to introduce any useful extension of the linear mixed model, e.g. an autoregressive process, into the model for the heterogeneity factors.

Finally, we will briefly discuss the relationship with ML estimation, largely following

Engel and Keen (1996) in the discussion of Lee and Nelder (1996). For ease of notation functional dependence on the unknown parameters is suppressed. The likelihood l(**y**) is obtained by integration of $\exp(L_c(\mathbf{y},\boldsymbol{\epsilon}))$ over the random effects $\boldsymbol{\epsilon} = (\mathbf{u}', \boldsymbol{\delta}')'$. This integral can be approximated by Laplace integration. To that end, $L_c$ is approximated by a quadratic function in $\boldsymbol{\epsilon}$ by Taylor expansion around $\bar{\boldsymbol{\epsilon}}$, where $[\partial L_c(\mathbf{y}, \mathbf{u})/\partial\boldsymbol{\epsilon}]_{\bar{\boldsymbol{\epsilon}}} = \mathbf{0}$. It follows that:

$$L(\mathbf{y}) = \log(l(\mathbf{y})) \approx L_c(\mathbf{y}, \bar{\boldsymbol{\epsilon}}) - \tfrac{1}{2}\log(\det(-[\partial^2 L_c(\mathbf{y}, \boldsymbol{\epsilon})/ \partial\boldsymbol{\epsilon}\partial\boldsymbol{\epsilon}']_{\bar{\boldsymbol{\epsilon}}})) - \tfrac{1}{2}m \log(2\pi),$$

where m is the number of elements of $\boldsymbol{\epsilon}$. This implies that the pdf f of $\boldsymbol{\epsilon}$ conditional upon **y** can be approximated by a normal pdf with mean $\bar{\boldsymbol{\epsilon}}$ and dispersion matrix $\boldsymbol{\Omega} = [-\partial^2 L_c(\mathbf{y}, \boldsymbol{\epsilon})/\partial\boldsymbol{\epsilon}\partial\boldsymbol{\epsilon}']^{-1}_{\bar{\boldsymbol{\epsilon}}}$ :

$$\log(f(\boldsymbol{\epsilon} \mid \mathbf{y})) = L_c(\mathbf{y}, \boldsymbol{\epsilon}) - L(\mathbf{y}) \approx -\tfrac{1}{2}(\boldsymbol{\epsilon}-\bar{\boldsymbol{\epsilon}})'\boldsymbol{\Omega}^{-1}(\boldsymbol{\epsilon}-\bar{\boldsymbol{\epsilon}}) - \tfrac{1}{2}\log(\det(\boldsymbol{\Omega})) - \tfrac{1}{2}m \log(2\pi).$$

Employing this normal approximation in the estimating equations for $\boldsymbol{\alpha} = (\mathbf{b}', \boldsymbol{\beta}')'$:

$\mathbf{0} = \partial L_c(\mathbf{y}, \boldsymbol{\epsilon})/\partial\boldsymbol{\alpha} \approx \partial L(\mathbf{y})/\partial\boldsymbol{\alpha} + (\partial\bar{\boldsymbol{\epsilon}}/\partial\boldsymbol{\alpha})\boldsymbol{\Omega}^{-1}(\boldsymbol{\epsilon}-\bar{\boldsymbol{\epsilon}})$, and for predictions for $\boldsymbol{\epsilon}$:

$$\mathbf{0} = \partial L_c(\mathbf{y}, \boldsymbol{\epsilon})/\partial\boldsymbol{\epsilon} = \partial f(\boldsymbol{\epsilon} \mid \mathbf{y})/\partial\boldsymbol{\epsilon} \approx -\boldsymbol{\Omega}^{-1}(\boldsymbol{\epsilon}-\bar{\boldsymbol{\epsilon}}).$$

It follows that $\hat{\boldsymbol{\alpha}} = (\hat{\mathbf{b}}', \hat{\boldsymbol{\beta}}')'$ approximates the ML estimator, while predictions $\hat{\boldsymbol{\epsilon}} = (\hat{\mathbf{u}}', \hat{\boldsymbol{\delta}}')' = \bar{\boldsymbol{\epsilon}}$ approximate $E(\boldsymbol{\epsilon} \mid \mathbf{y})$, evaluated at $\hat{\boldsymbol{\alpha}}$. The ML equation (Louis, 1982) for $\sigma^2_{\delta}$ is:

$$E(\partial L_c(\mathbf{y}, \boldsymbol{\epsilon})/\partial\sigma^2_{\delta} \mid \mathbf{y}) = \tfrac{1}{2}\,\sigma^{-4}_{\delta}\, E(\boldsymbol{\delta}'\mathbf{R}^{-1}\boldsymbol{\delta} \mid \mathbf{y}) - \tfrac{1}{2}\, q\sigma^{-2}_{\delta} = 0, \text{ leading to}$$

$$\sigma^2_{\delta} = \{E(\boldsymbol{\delta} \mid \mathbf{y})'\mathbf{R}^{-1}E(\boldsymbol{\delta} \mid \mathbf{y}) + \text{trace}(\mathbf{R}^{-1}\,\text{Var}(\boldsymbol{\delta} \mid \mathbf{y}))\} \;/\; q.$$

Now, in the normal approximation for $(\boldsymbol{\epsilon} \mid \mathbf{y})$, first matrix $\boldsymbol{\Omega}$ is replaced by $[-E(\partial^2 L_c(\mathbf{y}, \boldsymbol{\epsilon})/\partial\boldsymbol{\epsilon}\partial\boldsymbol{\epsilon}' \mid \boldsymbol{\epsilon})]^{-1}_{\bar{\boldsymbol{\epsilon}}}$, which simplifies the part corresponding to $\boldsymbol{\delta}$, and second the (sparse) upper right-hand and lower left-hand parts, involving derivatives with respect to elements of both **u** and $\boldsymbol{\delta}$, are ignored in taking the inverse. This way, $\text{Var}(\boldsymbol{\delta} \mid \mathbf{y})$ is approximated by $(\mathbf{DWD}' + \mathbf{R}^{-1}\sigma^2_{\delta})^{-1}$. Finally, as an approximate REML correction for estimation of $\boldsymbol{\beta}$, this last expression is replaced by **C**. This yields (7). Update (8) for $\rho$ is chosen as an analagon of (7). Since $\beta$ is an overall residual variance, in a future implementation, a REML correction for $\beta$ may be considered as well.

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# Chapter 10

## IRREML and ML

Based on:

Engel, B., Keen, A. (1996). Contribution to the discussion of Lee and Nelder (1996). Hierarchical Generalized Linear Models. *Journal of the Royal Statistical Society* B **58**, 656-657

and

Engel, B., Keen, A. (1996). An introduction to generalized linear mixed models. Invited paper. *Proceedings XIIIth International Biometric Conference*. Amsterdam.

The approximate relationship between IRREML and maximum likelihood estimation is discussed in some detail. A simple example is presented to illustrate inconsistency of IRREML variance component estimators under certain asymptotic conditions.

## 1 A general outline of the relationship between IRREML and ML

It will be shown that estimation by IRREML can be derived as an approximation to ML estimation. For ease of notation attention is restricted to one component of variance $\sigma_u^2$ for random effects $u_1 \ldots u_q$ collected in vector $\mathbf{u}$. Let $f(\mathbf{y} \mid \mathbf{u})$ be the pdf of $\mathbf{y}$ conditional upon $\mathbf{u}$ with unknown vector of parameters $\boldsymbol{\beta}$ and let $k(\mathbf{u})$ be the pdf of $\mathbf{u}$ with unknown parameter $\sigma_u^2$. To simplify the notation, functional dependence of the pdf's on the unknown parameters is suppressed. Let

$$h(\mathbf{y},\mathbf{u}) = \log(f(\mathbf{y} \mid \mathbf{u})) + \log(k(\mathbf{u}))$$

be the logarithm of the joint pdf of $\mathbf{y}$ and $\mathbf{u}$. The likelihood $l(\mathbf{y})$ is:

$$l(\mathbf{y}) = \int \ldots \int \exp(h(\mathbf{y},\mathbf{u}))\, d\mathbf{u}.$$

We start with estimation of $\boldsymbol{\beta}$ (and prediction of $\mathbf{u}$). For fixed $\sigma_u^2$, from a well known property of efficient scores, ML equations for $\boldsymbol{\beta}$ are (see also Louis, 1982):

$$\partial \log(l(\mathbf{y}))/\partial\boldsymbol{\beta} = \partial \log(l(\mathbf{y}))/\partial\boldsymbol{\beta} + E(\partial \log(r(\mathbf{u} \mid \mathbf{y}))/\partial\boldsymbol{\beta} \mid \mathbf{y}) = E(\partial h(\mathbf{y},\mathbf{u})/\partial\boldsymbol{\beta} \mid \mathbf{y}) = \mathbf{0},$$

where $r(\mathbf{u} \mid \mathbf{y})$ is the pdf of $\mathbf{u}$ conditional upon $\mathbf{y}$, i.e. $\log(l(\mathbf{y})) + \log(r(\mathbf{u} \mid \mathbf{y})) = h(\mathbf{y},\mathbf{u})$. For normal $\mathbf{u}$, the IRREML equations for $\boldsymbol{\beta}$ and $\mathbf{u}$ are:

$$\partial h(\mathbf{y},\mathbf{u})/\partial\boldsymbol{\beta} = \mathbf{0}, \tag{1}$$

$$\partial h(\mathbf{y},\mathbf{u})/\partial\mathbf{u} = \mathbf{0}. \tag{2}$$

The latter equation is equivalent to:

$$\partial \log(r(\mathbf{u} \mid \mathbf{y}))/\partial\mathbf{u} = \mathbf{0}. \tag{3}$$

When equations $\partial h(\mathbf{y},\mathbf{u})/\partial\boldsymbol{\beta} = \mathbf{0}$ are linear in some monotonic function $m(\mathbf{u})$ and $m(.)$ evaluated at the mode of $(\mathbf{u} \mid \mathbf{y})$ equals the mean of $(m(\mathbf{u}) \mid \mathbf{y})$, it directly follows that the ML and IRREML estimators for $\hat{\beta}$ are the same and that $m(.)$ evaluated at the solution $\hat{\mathbf{u}}$ of (2) (or (3)) is a prediction of the form $m(\hat{\mathbf{u}}) = E(m(\mathbf{u}) \mid \mathbf{y})$ evaluated for the ML / IRREML estimate $\hat{\boldsymbol{\beta}}$. For non-normal $\mathbf{u}$, the same argument (Engel and Keen, 1996) holds for Lee and Nelder's (1996) hierarchical likelihood estimators for $\boldsymbol{\beta}$ and $\mathbf{u}$ that maximize $h(\mathbf{y},\mathbf{u})$.

Now, with the Laplace integral approximation, temporarily suppressing dependence upon y in the notation:

$$l = \int \ldots \int \exp(h(\mathbf{u}))\, d\mathbf{u} \approx \int \ldots \int \exp(h(\tilde{\mathbf{u}}) + \tfrac{1}{2}(\mathbf{u}-\tilde{\mathbf{u}})' h''(\tilde{\mathbf{u}})(\mathbf{u}-\tilde{\mathbf{u}}))\, d\mathbf{u} =$$

$$(2\pi)^{\frac{1}{2}q} \sqrt{\det((-h''(\tilde{\mathbf{u}}))^{-1})} \exp(h(\tilde{\mathbf{u}})) \times$$
$$\times \int \ldots \int \exp(-\tfrac{1}{2}(\mathbf{u}-\tilde{\mathbf{u}})'(-h''(\tilde{\mathbf{u}}))(\mathbf{u}-\tilde{\mathbf{u}}))\, (2\pi)^{-\frac{1}{2}q}\, (1/\sqrt{\det((-h''(\tilde{\mathbf{u}}))^{-1})})\, d\mathbf{u} =$$

$$(2\pi)^{\frac{1}{2}q} \sqrt{\det((-h''(\tilde{\mathbf{u}}))^{-1})} \exp(h(\tilde{\mathbf{u}})),$$

where $h'(\tilde{\mathbf{u}}) = [\partial h(\mathbf{u})/\partial \mathbf{u}]_{\tilde{\mathbf{u}}} = \mathbf{0}$, and $h''(\tilde{\mathbf{u}})$ denotes the matrix of second order partial derivatives with respect to $\mathbf{u}$ evaluated at $\tilde{\mathbf{u}}$. Note that $\tilde{\mathbf{u}}$ is a function of both $\mathbf{y}$ and $\boldsymbol{\beta}$. It follows that:

$$\log(r(\mathbf{u} \mid \mathbf{y})) \approx h(\mathbf{y},\mathbf{u}) - h(\mathbf{y},\tilde{\mathbf{u}}) - \tfrac{1}{2}\log(\det((-h''(\tilde{\mathbf{u}}))^{-1})) - \tfrac{1}{2}q \log(2\pi) \approx$$
$$- \tfrac{1}{2}(\mathbf{u}-\tilde{\mathbf{u}})' (-h''(\tilde{\mathbf{u}})) (\mathbf{u}-\tilde{\mathbf{u}}) - \tfrac{1}{2}\log(\det(-h''(\tilde{\mathbf{u}})^{-1})) - \tfrac{1}{2}q \log(2\pi) =$$
$$- \tfrac{1}{2}(\mathbf{u}-\tilde{\mathbf{u}})' \boldsymbol{\Omega}^{-1} (\mathbf{u}-\tilde{\mathbf{u}}) - \tfrac{1}{2}\log(\det(\boldsymbol{\Omega})) - \tfrac{1}{2}q \log(2\pi),$$

where $\boldsymbol{\Omega} = (-h''(\tilde{\mathbf{u}}))^{-1}$. So, approximately:

$$(\mathbf{u} \mid \mathbf{y}) \sim N(\tilde{\mathbf{u}}, \boldsymbol{\Omega}).$$

When $f(\mathbf{y} \mid \mathbf{u})$ is from the GLM exponential family:

$$h'(\mathbf{u}) = \partial \log(f(\mathbf{y} \mid \mathbf{u}))/\partial \mathbf{u} - \sigma_u^{-2}\, \mathbf{u} \quad \text{and}$$
$$h''(\mathbf{u}) = \mathbf{Z}'\mathbf{W}g'(\boldsymbol{\mu})'(\partial(\mathbf{y}-\boldsymbol{\mu})/\partial \mathbf{u}) + \mathbf{Z}'(\partial(\mathbf{W}g'(\boldsymbol{\mu}))/\partial \mathbf{u})(\mathbf{y}-\boldsymbol{\mu}) - \sigma_u^{-2}\mathbf{I}.$$

Here, $\mathbf{W}$ is the diagonal matrix of iterative weights $\{g'(\mu)^2 V(\mu)\}^{-1}$, $g(.)$ is the link function and $V(.)$ the variance function. The second term on the right-hand side equals 0 for a canonical link function, e.g. for the logit link for binomial data or log link for Poisson data, and its expectation conditional upon $\mathbf{u}$ equals $\mathbf{0}$ for any link function. Replacing $\boldsymbol{\Omega}$ by $\boldsymbol{\Omega}_*$ $= [E(-h''(\mathbf{u}) \mid \mathbf{u})]_{\tilde{\mathbf{u}}}^{-1} = [\mathbf{Z}'\mathbf{W}\mathbf{Z} + \sigma_u^{-2}\mathbf{I}]_{\tilde{\mathbf{u}}}^{-1}$, and ignoring the functional dependence of $\boldsymbol{\Omega}_*$ on $\boldsymbol{\beta}$ through the matrix of iterative weights $\mathbf{W}$, it follows from (2) and (3) that approximately:

$$\partial h(\mathbf{y},\mathbf{u})/\partial \boldsymbol{\beta} = \partial \log(l(\mathbf{y}))/\partial \boldsymbol{\beta} + (\partial \tilde{\mathbf{u}}/\partial \boldsymbol{\beta})\boldsymbol{\Omega}_*^{-1}(\mathbf{u}-\tilde{\mathbf{u}}) \quad \text{and}$$
$$\partial h(\mathbf{y},\mathbf{u})/\partial \mathbf{u} = - \boldsymbol{\Omega}_*^{-1}(\mathbf{u}-\tilde{\mathbf{u}}).$$

Hence, the IRREML estimator $\hat{\boldsymbol{\beta}}$ from (1) and (2) (or (3)) approximates the ML estimator, while $\hat{\mathbf{u}} = \tilde{\mathbf{u}} \approx E(\mathbf{u} \mid \mathbf{y})$ evaluated at $\hat{\boldsymbol{\beta}}$.

Now, consider estimation of $\sigma_u^2$. The ML equation for $\sigma_u^2$ is:

$$E(\partial h(\mathbf{y},\mathbf{u})/\partial \sigma_u^2 \mid \mathbf{y}) = E(\partial \log(k(\mathbf{u}))/\partial \sigma_u^2 \mid \mathbf{y}) = 0.$$

For normal $\mathbf{u}$ this is equivalent to:

$$- q / (2\sigma_u^2) + E(\mathbf{u}'\mathbf{u} \mid \mathbf{y}) / (2\sigma_u^4) = 0, \text{ or}$$
$$\sigma_u^2 = \{E(\mathbf{u} \mid \mathbf{y})'E(\mathbf{u} \mid \mathbf{y}) + \text{trace}(\text{Var}(\mathbf{u} \mid \mathbf{y}))\} / q \approx (\hat{\mathbf{u}}'\hat{\mathbf{u}} + \text{trace}(\mathbf{T})) / q. \quad (4)$$

Here, q is the number of elements of $\mathbf{u}$ and $\mathbf{T}$ is the part of the inverse of the coefficient matrix of the mixed model equations in terms of the adjusted dependent variate $\zeta$ that corresponds to the random effects. $\mathbf{T}$ replaces $\boldsymbol{\Omega}_*$, because now estimation of $\boldsymbol{\beta}$ is taken into account as well, as a "REML type" adjustment of the ML equations. Solving the equation iteratively yields the EM type algorithm for the IRREML estimator (see expression (11) in Chapter 6). For non-normal $\mathbf{u}$, a similar argument can be followed after $\log(k(\mathbf{u}))$ is approximated by a second order Taylor expansion around $\hat{\mathbf{u}}$.

The kernel of the log likelihood L is approximately equal to:

$$L \approx -\tfrac{1}{2} \log(\det(\mathbf{Z}'\mathbf{W}\mathbf{Z}+\sigma_u^{-2}\mathbf{I})) - \tfrac{1}{2} \hat{D} - \tfrac{1}{2} \hat{\mathbf{u}}'\hat{\mathbf{u}} / \sigma_u^2 - \tfrac{1}{2} q \log(\sigma_u^2), \quad (5)$$

where $D = -2\log(f(\mathbf{y} \mid \mathbf{u}))$ is the conditional deviance, and $\hat{D}$ is D evaluated at $\hat{\mathbf{u}}$.

Following Breslow and Clayton (1993), further approximation of L is possible, offering an alternative derivation leading to the IRREML algorithm. First, consider D for a single observation y:

$$D \propto -2 \int_y^{\mu} (y-t)/V(t)\, dt.$$

This is the area between y and $\mu$ on the t-axis and the curve $2(y-t) / V(t)$. It may be approximated by the area $(y-\mu)^2/V(\mu)$ of the triangle between y and $\mu$ on the t-axis and the point $(\mu, 2(y-\mu) / V(\mu))$. This suggests that D may be replaced by Pearson's generalized chi-square statistic: $\Sigma(y-\mu)^2/V(\mu)$. Next, we add $-\tfrac{1}{2}\log(\det(\mathbf{W}^{-1}))$, again ignoring dependence of $\mathbf{W}$ on $\boldsymbol{\beta}$, and treating the extra term as a constant. Now, employing (for details see Engel, 1989, p57, A5 (ii) and (iii); p82, C6):

$$\log(\det(\mathbf{Z}'\mathbf{W}\mathbf{Z} + \sigma_u^{-2}\mathbf{I})) + \log(\det(\mathbf{W}^{-1})) + q \log(\sigma_u^2) = \log(\det(\mathbf{H})),$$

where $\mathbf{H} = \mathbf{Z}\mathbf{Z}'\sigma_u^2 + \mathbf{W}^{-1}$, and

$$\Sigma(y-\mu)^2/V(\mu) + \hat{\mathbf{u}}'\hat{\mathbf{u}} / \sigma_u^2 = (\zeta-\hat{\eta})'\mathbf{W}^{-1}(\zeta-\hat{\eta}) + \hat{\mathbf{u}}'\hat{\mathbf{u}} / \sigma_u^2 =$$
$$(\zeta-\hat{\eta})'\mathbf{W}^{-1}(\zeta-\hat{\eta}) + \hat{\mathbf{u}}'\mathbf{Z}'(\zeta-\hat{\eta}) = (\zeta-\mathbf{X}\hat{\boldsymbol{\beta}})'\mathbf{W}^{-1}(\zeta-\mathbf{X}\hat{\boldsymbol{\beta}}-\mathbf{Z}\hat{\mathbf{u}}) = (\zeta-\mathbf{X}\hat{\boldsymbol{\beta}})'\mathbf{H}^{-1}(\zeta-\mathbf{X}\hat{\boldsymbol{\beta}}),$$

it follows that the kernel of the log likelihood is approximately equal to:

$$- \tfrac{1}{2} (\zeta-\mathbf{X}\hat{\boldsymbol{\beta}})'\mathbf{H}^{-1}(\zeta-\mathbf{X}\hat{\boldsymbol{\beta}}) - \tfrac{1}{2} \log(\det(\mathbf{H})).$$

The last expression is the kernel of the log likelihood obtained when the adjusted dependent variate $\zeta$ is assumed to be normally distributed with mean $\mathbf{X}\boldsymbol{\beta}$ and variance-covariance matrix $\mathbf{H}$. Following Breslow and Clayton (1993), adding a REML adjustment term $-\frac{1}{2}\log(\det(\mathbf{X}'\mathbf{H}^{-1}\mathbf{X}))$, updating the component of variance from this approximation yields the IRREML algorithm, with the same final estimates as from iteration based on (4).

When there is a multiplicative dispersion factor $\tau$ in the conditional variance of observations y, and the conditional error distribution is not fully specified, an extended quasi-likelihood (McCullagh and Nelder, 1989, Ch. 9; Nelder and Pregibon, 1987) may be defined. The extended quasi-likelihood is obtained by replacing $\log(f(\mathbf{y} \mid \mathbf{u}))$ by a (conditional) quasi-likelihood $Q(\mathbf{y} \mid \mathbf{u})$ and adding a term $-\frac{1}{2} \Sigma \log(2\pi\tau V(y))$ for estimation of $\tau$. The same approximations as before can be carried through, with D a (conditional) quasi-deviance, when $\mathbf{H}$ is redefined as: $\mathbf{H} = \mathbf{Z}\mathbf{Z}'\sigma_u^2 + \mathbf{W}^{-1}\tau$.

## 2 A simple illustration

Consider a GLMM for binary observations with a probit link, q independent normally distributed random effects $u_1 \ldots u_q$ with mean 0 and variance $\sigma_u^2$, and two binary observations $y_{i1}$ and $y_{i2}$ per random effect $u_i$, $i = 1 \ldots q$:

$$
\begin{aligned}
&(y_{ij} \mid u_i) \sim \text{Bernoulli}(\mu_i), \text{ conditionally independent, } j = 1, 2,\\
&\text{probit}(\mu_i) = \Phi^{-1}(\mu_i) = \eta_i = c + u_i,\\
&u_i \sim N(0,\sigma_u^2), \text{ independent, } i = 1 \ldots q.
\end{aligned}
$$

The overall mean c on the probit scale is the only fixed effect in the model. In Chapter 6 it is shown that this model can also be formulated as a threshold model for an underlying variable z:

$$z_{ij} = c + u_i + e_{ij},$$

where $u_i$, $e_{ij}$, $i = 1 \ldots q$, $j = 1, 2$, are independent and $e_{ij} \sim N(0, 1)$. We observe $y_{ij} = 1$ when $z_{ij} > 0$ and $y_{ij} = 0$ otherwise.

The normal approximation for the pdf of $(\mathbf{u} \mid \mathbf{y})$ is the crucial point in the derivation of IRREML as an approximate ML procedure. Therefore, we will first take a look at the exact conditional pdf and its normal approximation. Let $r(u_i \mid y_{i1}, y_{i2})$ denote the conditional pdf of $(u_i \mid y_{i1}, y_{i2})$ and $k(u_i)$ the pdf of $u_i$. Then (where possible, dropping index i for ease of notation):

$$
\begin{aligned}
&r(u \mid y_1, y_2) = \{P(y=y_1 \mid u)\ P(y = y_2 \mid u)\ k(u)\} / E_u\{P(y=y_1 \mid u)\ P(y=y_2 \mid u)\ k(u)\} =\\
&\{\mu^x\ (1-\mu)^{2-x}\ \exp(-\tfrac{1}{2}\sigma_u^{-2}u^2)\ (\sigma_u\sqrt{2\pi})^{-1}\} / \{p^x\ (1-p)^{2-x} + (-1)^x\ \text{Var}(\mu)\},
\end{aligned}
$$

where $x_i = y_{i1} + y_{i2}$ and p is the marginal probability $P(y_{ij} = 1)$:

$$p = E(\mu) = P(y = 1) = P(z > 0) = \Phi(c/\sqrt{(1+\sigma_u^2)}) = \Phi(\lambda c),$$

where $\lambda = 1 / \sqrt{(1+\sigma_u^2)}$ is a shrinkage factor. Furthermore:

$$\begin{aligned} &Var(\mu) = Var(P(z > 0 \mid u)) = E_u(P(z > 0 \mid u)^2) - p^2 = \\ &E_u(P(z > 0, z' > 0 \mid u)) - p^2 = \Phi_2(\lambda c, \lambda c; \rho) - p^2 , \end{aligned}$$

where z and z′ are assumed to be i.i.d. conditional upon u, $\rho = \sigma_u^2/(1+\sigma_u^2)$ is the intraclass correlation on the underlying scale in the threshold model and $\Phi_2(a, b; \rho)$ denotes the bivariate normal cdf with zero means, unit variances and correlation ρ.

It is assumed that the "true values" of the parameters are: c = 0 and $\sigma_u^2 = 1/9$, which implies p = 0.5 and ρ = 0.1.

To determine the approximate conditional pdf, first the IRREML estimate for c and predictions for the random effects $u_1 \ldots u_q$ will be derived. To this end we maximize the logarithm of the joint pdf of observations and random effects:

$$\begin{aligned} &\Sigma\, h(y_1,y_2,u) = \Sigma\, \{\log(P(y=y_1 \mid u)) + \log(P(y=y_2 \mid u)) + \log(k(u))\} = \\ &\Sigma\, \{x \log(\mu) + (2-x) \log(1-\mu) - \tfrac{1}{2} u^2 / \sigma_u^2 - \tfrac{1}{2} \log(\sigma_u^2) - \tfrac{1}{2} \log(2\pi)\}. \end{aligned}$$

The estimating equations are:

$$\begin{aligned} &(x_i/\mu_i)\, \phi(c+u_i) - ((2-x_i)/(1-\mu_i))\, \phi(c+u_i) - u_i / \sigma_u^2 = 0,\ i = 1 \ldots q, \text{ and} \\ &\Sigma\, (x_i/\mu_i)\, \phi(c+u_i) - ((2-x_i)/(1-\mu_i))\, \phi(c+u_i) = 0, \end{aligned}$$

where $\phi(.)$ is the standard normal pdf. There are only three possible values for a prediction $\hat{u}$, depending on whether x equals 0, 1 or 2 and they will be denoted by $\xi_0$, $\xi_1$ and $\xi_2$, respectively. The limiting behaviour of IRREML for $q \to \infty$ will be studied. Under these conditions the second estimating equation implies that:

$$P_o\, \xi_0 + P_1\, \xi_1 + P_2\, \xi_2 = 0,$$

where, under the parameter values specified, $P_0 = P(x = 0) = \Phi_2(0, 0; 0.1) = 0.2659$, $P_1 = P(x = 1) = 1 - 2P_0 = 0.4681$ and $P_2 = P(x = 2) = P_0 = 0.2659$. It follows that:

$$\hat{c} = 0,\ \xi_0 = \xi,\ \xi_1 = 0 \text{ and } \xi_2 = -\xi,$$

where ξ is solved from the non-linear equation:

$$\xi = -2\ \phi(\xi)\ \sigma_u^2 / (1-\Phi(\xi)),$$

which yields, after straightforward iteration, $\xi = -0.15586$. We have now determined the approximate conditional means $E(u \mid y_1,y_2) = E(u \mid x)$.

Next, we derive approximate variances from the second order derivatives of $h(y_1,y_2,u)$:

$$h''(y_1,y_2,u) = -\{(x/\mu)-(2-x)/(1-\mu)\}\ (c+u)\ \phi(c+u) - \{(x/\mu^2)+(2-x)/(1-\mu)^2\}\ \phi(c+u)^2 - \sigma_u^{-2},$$

where (partial) differentiation is with respect to u. For $c = \hat{c} = 0$ this becomes:

$$h''(y_1,y_2,u) = -\{(x/\Phi(u))-(2-x)/(1-\Phi(u))\}u\phi(u)\ - \{(x/\Phi(u)^2)+(2-x)/(1-\Phi(u))^2\}\ \phi(u)^2 - \sigma_u^{-2}.$$

For the conditional mean, $E(x \mid u) = 2\mu = 2\Phi(u)$ implies that:

$$E(-h''(y_1,y_2,u) \mid u) = 2\ \phi(u)^2 / \{\Phi(u)(1-\Phi(u))\}\ + \sigma_u^{-2}.$$

Since the iterative weights are equal to $w = \phi(c+u)^2 / \{\Phi(c+u)(1-\Phi(c+u)\}$, this is equal to the diagonal element of $\mathbf{Z'WZ} + \sigma_u^{-2}\mathbf{I}$, as it should be, when evaluated for $\hat{c}$ and $\hat{u}_1 ... \hat{u}_q$. The "REML modification", i.e. employing submatrix **T** from (4), is of order $O(q^{-1})$. So for $q \rightarrow \infty$ this modification may be ignored. The approximate conditional variance $Var(u \mid y_1,y_2) = \nu^2(x)$ is:

$$\nu^2(x) = E(-h''(y_1,y_2,u) \mid u)^{-1} = [2\ \phi(\xi_x)^2 / \{\Phi(\xi_x)(1-\phi(\xi_x))\}\ + \sigma_u^{-2}]^{-1}.$$

The approximate pdf, conditional upon x, is:

$$\nu(x)^{-1}\ (2\pi)^{-½}\ \exp(-½(u-\xi_x)^2/\nu^2(x)).$$

Some function evaluations for the exact and approximate conditional pdf, on the log scale, are shown in Table 1. They seem to be well matched, but, as we shall see in a moment, not well enough for proper estimation of $\sigma_u^2$.

It was already noted in Chapter 6 that in this simple model IRREML underestimates $\sigma_u^2$ by about a factor ½. The equation to be solved for $\sigma_u^2$ is:

$$\sigma_u^2 = \{\Sigma\ \hat{u}_i^2 + \Sigma\ \nu^2(x_i)\}\ /\ q,$$

and for $q \rightarrow \infty$ this becomes

$$\sigma_u^2 = P_0\xi_0^2 + P_1\xi_1^2 + P_2\xi_2^2 + P_0\nu^2(0) + P_1\nu^2(1) + P_2\nu^2(2) =$$

**Table 1.** Comparing the exact and approximate conditional pdf on the log scale

| u | logpdf x = 0 | appr.logpdf x = 0 | logpdf x = 1 | appr.logpdf x = 1 | logpdf x = 2 | appr.logpdf x = 2 |
|---|---|---|---|---|---|---|
| -1.0000 | -3.341 | -3.411 | -4.882 | -4.891 | -6.678 | -6.610 |
| -0.9000 | -2.548 | -2.596 | -3.909 | -3.915 | -5.526 | -5.475 |
| -0.8000 | -1.852 | -1.884 | -3.038 | -3.042 | -4.479 | -4.443 |
| -0.7000 | -1.255 | -1.274 | -2.269 | -2.271 | -3.539 | -3.513 |
| -0.6000 | -0.757 | -0.767 | -1.603 | -1.603 | -2.703 | -2.686 |
| -0.5000 | -0.359 | -0.362 | -1.038 | -1.038 | -1.973 | -1.962 |
| -0.4000 | -0.061 | -0.061 | -0.576 | -0.576 | -1.347 | -1.340 |
| -0.3000 | 0.136 | 0.139 | -0.217 | -0.216 | -0.825 | -0.821 |
| -0.2000 | 0.232 | 0.235 | 0.040 | 0.040 | -0.407 | -0.404 |
| -0.1000 | 0.226 | 0.229 | 0.194 | 0.194 | -0.093 | -0.091 |
| 0.0000 | 0.118 | 0.121 | 0.245 | 0.246 | 0.118 | 0.121 |
| 0.1000 | -0.093 | -0.091 | 0.194 | 0.194 | 0.226 | 0.229 |
| 0.2000 | -0.407 | -0.404 | 0.040 | 0.040 | 0.232 | 0.235 |
| 0.3000 | -0.825 | -0.821 | -0.217 | -0.216 | 0.136 | 0.139 |
| 0.4000 | -1.347 | -1.340 | -0.576 | -0.576 | -0.061 | -0.061 |
| 0.5000 | -1.973 | -1.962 | -1.038 | -1.038 | -0.359 | -0.362 |
| 0.6000 | -2.703 | -2.686 | -1.603 | -1.603 | -0.757 | -0.767 |
| 0.7000 | -3.539 | -3.513 | -2.269 | -2.271 | -1.255 | -1.274 |
| 0.8000 | -4.479 | -4.443 | -3.038 | -3.042 | -1.852 | -1.884 |
| 0.9000 | -5.526 | -5.475 | -3.909 | -3.915 | -2.548 | -2.596 |
| 1.0000 | -6.678 | -6.610 | -4.882 | -4.891 | -3.341 | -3.411 |

$$2P_0(\xi^2+\nu^2(0)) + (1-2P_0)\nu^2(1). \qquad (6)$$

This equation is nearly solved by the true value 1/9 for the component, but as the plot of the right-hand side of (6) against various values of $\sigma_u^2$ in Figure 1 shows, this holds for many values for the component. The solution of (6) can be obtained by simple iteration, as shown in Table 2. The program shown is in Genstat 5 (1993) and self explanatory. The solution is $\hat{\sigma}_u^2 = 0.05245$, which indeed nearly equals half of the true value.

How does maximum likelihood estimation work out in this simple setting? The log likelihood is:

$$L = \Sigma \log(\int P(y=y_1 \mid u)P(y=y_2 \mid u)k(u)\ du) = \Sigma \log(p^x\ (1-p)^{2-x} + (-1)^x\ \mathrm{Var}(\mu)).$$

The ML estimator for c converges to 0 for $q \to \infty$. The profile log likelihood for $\sigma_u^2$ (substitute p = ½) divided by q converges to:

$$2P_0\ \log(\Phi_2(0,0;\rho)) + (1-2P_0)\ \log(½-\Phi_2(0,0;\rho)).$$

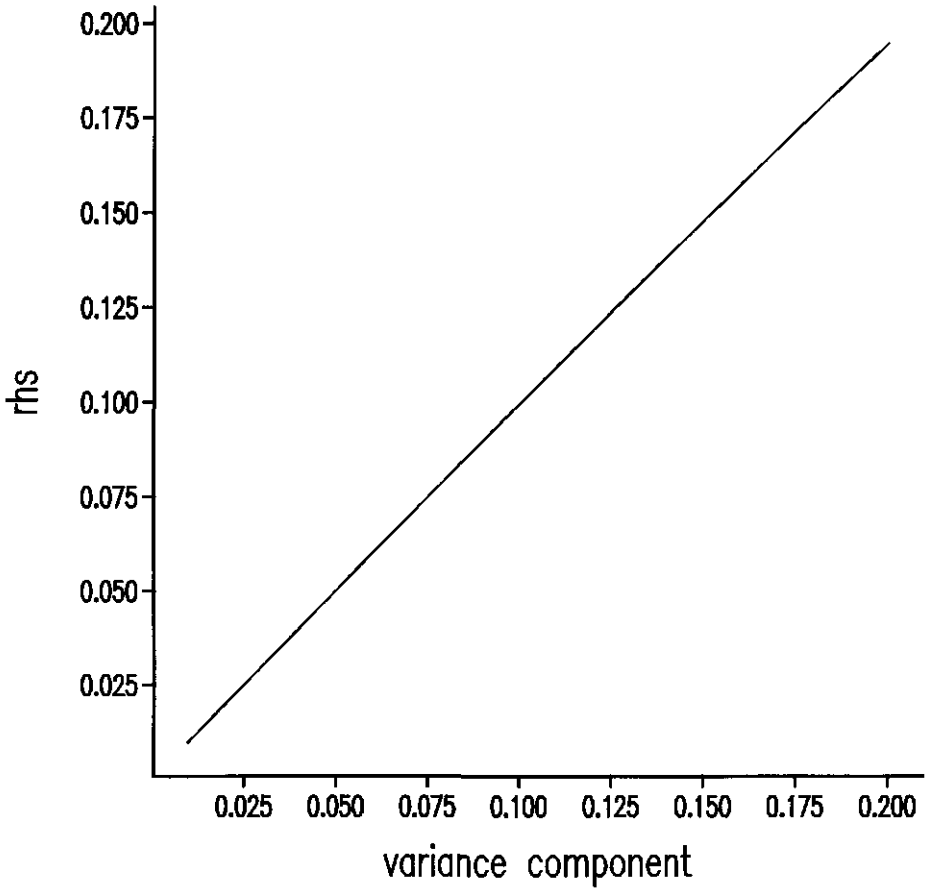


**Figure 1** Right-hand side of expression (6) versus variance component

**Table 2. Solving for the component of variance**

```
JOB 'variance component'
CALC P0=CLBVARIATENORMAL(0;0;0.1)
CALC var   = 0.11111
CALC u0    = -0.15586
CALC pi    = C('pi')
CALC iter  = 0
FOR[ntimes = 2500]
```

```
  FOR[ntimes = 5]
    CALC u0   = -2*var*(EXP(-u0*u0/2)/SQRT(2*pi))/CUNORMAL(u0)
  ENDFOR
  CALC v0   = (2*EXP(-u0*u0)/(2*pi))
  CALC v0   = (v0/CLNORMAL(u0))/CUNORMAL(u0) + (1/var)
  CALC v0   = 1/v0
  CALC v1   = 1 / ((4/pi) + (1/var))
  CALC var  = 2*P0*(u0*u0+v0)+(1-2*P0)*v1
  CALC iter = iter+1
  CALC crit = 50*INTEGER(iter/50)-iter
  IF (crit.EQ.0)
    PRIN iter, u0, var
  ENDIF
ENDFOR
STOP
```

| iteration | $\hat{u}$ at x=0 | $\hat{\sigma}_u^2$ |
|---|---|---|
| 0 | -0.1559 | 0.1111 |
| 50 | -0.1251 | 0.08657 |
| 100 | -0.1104 | 0.07554 |
| 150 | -0.1018 | 0.06920 |
| 200 | -0.09615 | 0.06510 |
| 250 | -0.09221 | 0.06225 |
| 300 | -0.08933 | 0.06017 |
| 350 | -0.08716 | 0.05861 |
| 400 | -0.08549 | 0.05741 |
| 450 | -0.08419 | 0.05648 |
| 500 | -0.08315 | 0.05574 |
| 600 | -0.08164 | 0.05466 |
| 700 | -0.08065 | 0.05396 |
| 800 | -0.07999 | 0.05349 |
| 900 | -0.07953 | 0.05316 |
| 1000 | -0.07922 | 0.05294 |
| 1250 | -0.07880 | 0.05265 |
| 1500 | -0.07864 | 0.05253 |
| 1750 | -0.07857 | 0.05248 |
| 2000 | -0.07854 | 0.05246 |
| 2250 | -0.07853 | 0.05245 |
| 2500 | -0.07852 | 0.05245 |

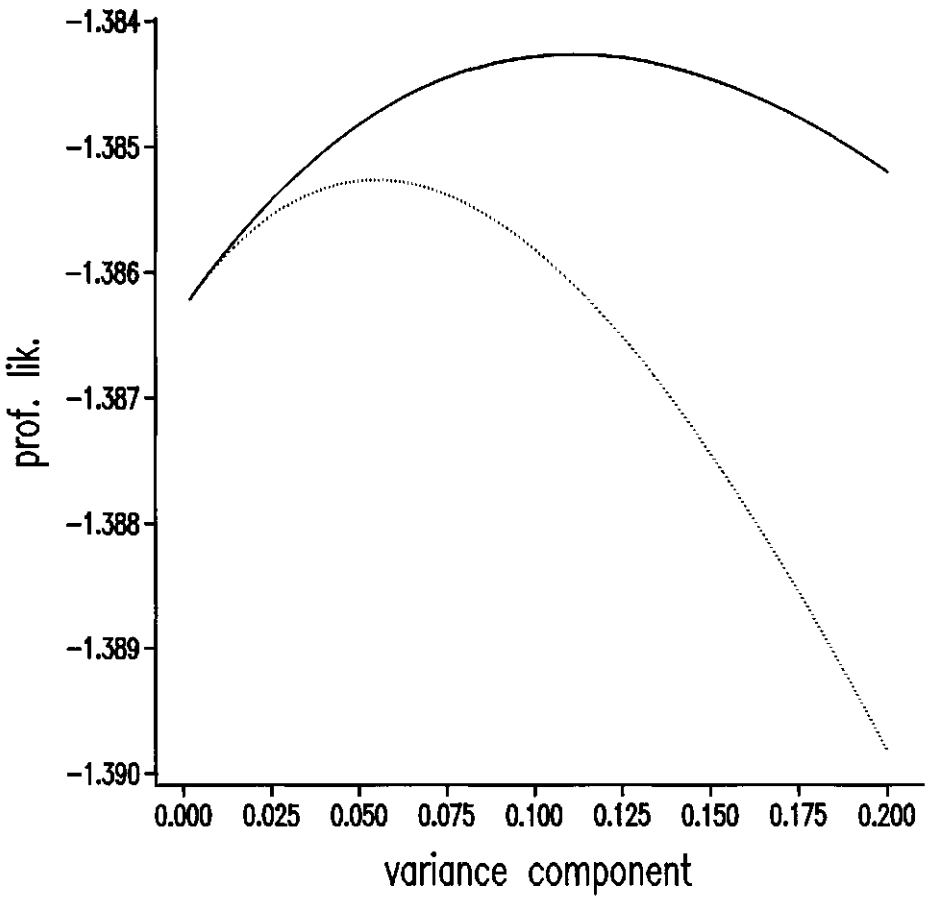


**Figure 2** The profile likelihood for $\sigma_u^2$ (___) (divided by q) and its Laplace approximation (...) for $q \to \infty$.

The ML equation is:

$$\Phi_2(0,0;\rho) = P_0,$$

which yields the correct answer $\rho = 0.1$. Hence, the ML estimator for $\sigma_u^2$, in contrast to the IRREML estimator, is consistent. In Figure 2 the profile likelihood for $\sigma_u^2$ and its Laplace approximation, for $q \to \infty$, are plotted. Clearly, the two curves are markedly different. Obviously, consistency ($q \to \infty$) will also hold for a posterior mode estimator. This suggests that in more realistic problems, where the asymptotics $q \to \infty$ apply, the Gibbs sampler may produce more acceptable estimates.

We will finish with a brief look at GAR and MQL (see Chapter 6). In the QL equation for $c_* = \lambda c$ (see Chapter 6), matrix **D** equals $\phi(c_*)\mathbf{1}_{2q}$, where $\mathbf{1}_{2q}$ is a vector with 2q elements which are all equal to 1. Var(**y**) is a block diagonal matrix, and blocks are approximated by:

$$\begin{pmatrix} p(1-p) & \phi(c_*)^2\rho \\ \phi(c_*)^2\rho & p(1-p) \end{pmatrix}.$$

The solution is: $\hat{c}_* = \Phi^{-1}(\bar{y})$, i.e. $\hat{p} = \bar{y}$. The adjusted dependent variate and weights are:

$$\zeta_{GAR} = \hat{c}_* + (y-\hat{p}) / \phi(\hat{c}_*) \quad \text{and} \quad w_{GAR} = \phi(\hat{c}_*)^2 / \{\hat{p}(1-\hat{p}) - \rho\phi(\hat{c}_*)^2\} = f/(1-\rho f),$$

where $f = \phi(\hat{c}_*)^2 / \{\hat{p}(1-\hat{p})\}$. The mixed model equations in terms of $\zeta_{GAR}$ are:

$$\begin{pmatrix} 2qf/(1-\rho f) & 2f/(1-\rho f)\mathbf{1}_q' \\ 2f/(1-\rho f)\mathbf{1}_q & ((2f/(1-\rho f)) + \rho^{-1})\mathbf{I}_q \end{pmatrix} \begin{pmatrix} c_* \\ \mathbf{u}_* \end{pmatrix} = \begin{pmatrix} (2qf/(1-\rho f))(\hat{c}_* + (y-\hat{p})/\phi(\hat{c}_*)) \\ (2f/(1-\rho f))(\bar{y}_1 - \hat{p} \ldots \bar{y}_q - \hat{p})' + (2f/(1-\rho f))\hat{c}_*\mathbf{1}_q \end{pmatrix},$$

where $\mathbf{u}_* = \lambda\mathbf{u}$ and $\hat{c}_*$ and $\hat{p}$ are evaluated for the current iterates. It is not hard to show that this is equivalent to iteratively solving:

$$\begin{pmatrix} 2q & 2\mathbf{1}_q' \\ 2\mathbf{1}_q & (2+\psi)\mathbf{I}_q \end{pmatrix} \begin{pmatrix} p \\ \mathbf{u}_{**} \end{pmatrix} = \begin{pmatrix} 2q\bar{y} \\ (2\bar{y}_1 \ldots 2\bar{y}_q)' \end{pmatrix},$$

where $\mathbf{u}_{**} = \mathbf{u}_* \phi(c_*)$, $\psi = (1-\rho f) / (\rho f)$ and $\bar{y}_i = \frac{1}{2} x_i$. These are the mixed model equations as if the data were following a LMM with a "between" component of variance $\phi(c_*)^2\rho = f\rho p(1-p)$, "residual variance" $(1-f\rho)p(1-p)$ and "total variance" $p(1-p)$. They yield solutions for p and $u_{**}$. The intra-class correlation corresponding to these equations is a multiple f of $\rho$ (see Gilmour, Anderson and Rae (1985) for references to Robertson's correction factor f). Solutions are: $\hat{p}_{GAR} = \bar{y}$, $\hat{c}_{*\,GAR} = \Phi^{-1}(\bar{y})$ and $\hat{u}_{i\,GAR} = 2\,(2+\psi)^{-1}\,\phi(\hat{c}_*)^{-1}\,(\bar{y}_i - \bar{y})$, $i = 1 \ldots q$. In the EM type update for $\rho$ (see Chapter 6): $\text{trace}(\mathbf{T}) = \rho\,(n+q\psi)\,(n+\psi)^{-1}$. After substitution it follows that:

$$\hat{\rho}_{GAR} = \{MS_{Between} - \bar{y}(1-\bar{y})\} / \phi(\Phi^{-1}(\bar{y}))^2,$$

where $MS_{Between}$ is the "mean square between random effects u" for the original binary observations. When the Taylor approximation for the bivariate normal cdf (see Chapter 6) holds, this estimator is nearly consistent ($q \to \infty$). The same estimator is found when

Pearson's chi-square statistic is set equal to its degrees of freedom (Williams, 1982).

Now, once we know that GAR is nearly consistent, it is simple to make plausible that IRREML under-estimates by $\frac{1}{2}\sigma_u^2$. We already noted that $w_{GAR} = \phi(c_*)^2 / \{p(1-p)-\rho\phi(c_*)^2\}$, which in this case is equal to: $(\frac{1}{2}\pi - \sigma_u^2)^{-1}$. This amounts to a "residual variance" $(\frac{1}{2}\pi - \sigma_u^2)$ in the approximate LMM for $\zeta_{GAR}$. For IRREML: $w_{IRREML} = \phi(c)^2 / \{\mu(1-\mu)\}$, which equals $2/\pi$, when we start with all random effects equal to 0 and $\hat{p} = \bar{y} \approx \frac{1}{2}$. This amounts to a residual variance $\frac{1}{2}\pi$ for $\zeta_{IRREML}$. The adjusted dependent variates for IRREML and GAR are the same for the starting values assumed. In this example IRREML is equivalent to iterated re-weighted ANOVA. $\sigma_u^2$ is estimated by subtracting the residual variance from the mean sum of squares between pairs of observations and dividing by 2. Hence, we subtract $\frac{1}{2}\sigma_u^2$ too much and consequently the IRREML estimator for $\sigma_u^2$ is $\frac{1}{2}\hat{\sigma}_u$ too low. The same can be expected to hold for MQL since $w_{MQL} = \phi(c_*)^2 / \{p(1-p)\}$. Obviously, the approximation for Var(**y**) is extremely important for the performance of the variance component estimator. GAR will do well as long as the Taylor expansion for the bivariate cdf holds, i.e. as long as $\rho$ is small and p is not too extreme (see Gilmour, Anderson and Rae, 1985). MQL fails because of the poor approximation to Var(**y**).

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## Summary

This dissertation was born out of a need for general and numerically feasible procedures for inference in variance components models for non-normal data. The methodology should be widely applicable within the institutes of the Agricultural Research Department (DLO) of the Dutch Ministry of Agriculture, Nature Management and Fisheries. Available methodology employing maximum likelihood estimation, due to numerical limitations, was too restricted with respect to the choice of random structures. Modification of the iterative re-weighted least squares (IRLS) algorithm, which is widely used for estimation in generalized linear models (GLMs), seemed a promising alternative to maximum likelihood.

The class of generalized linear mixed models (GLMMs) studied in this dissertation, is a straightforward extension of GLMs. The proposed estimation procedure for GLMMs, obtained by replacing least squares by linear mixed model (LMM) methodology, is a straightforward extension of the IRLS procedure for GLMs. The new procedure, involves iterative use of restricted maximum likelihood (REML) and is referred to as iterative re-weighted restricted maximum likelihood (IRREML). REML is an estimation procedure for ordinary normal data LMMs. Software for REML is widely available. In this thesis facilities for REML in the statistical programming language Genstat 5 are employed. In each iteration step of IRREML, REML is applied to an approximate LMM for an artificial dependent variate. This variate and corresponding residual weights, referred to as the "adjusted dependent variate" and the "iterative weights" (adhering to GLM terminology), are up-dated after each iteration. Numerical restrictions for IRREML are the same as for REML for ordinary normal data mixed models and pertain to the size of matrices to be inverted. These can be dealt with to a large extent by eliminating (absorbing) factors with a large number of levels. The estimation procedure, programmed in Genstat 5, is available through the Genstat Procedure Library of the Agricultural Mathematics Group (GLW-DLO). By now it has been widely used both within and outside the institutes of DLO.

After the introduction in Chapter 1, inference for LMMs, with emphasis on REML, and for over-dispersed GLMs, illustrating maximum quasi-likelihood estimation, is discussed in Chapters 2 and 3.

IRREML is introduced in Chapter 4. As can be seen from the discussion in that chapter, and from later chapters, a number of statisticians independently have approached the estimation problem from different starting points, ending up with the same estimating equations. A Bayesian approach for prediction of random (genetic) effects for binary, binomial and ordinal data, was presented as early as 1983 by Gionola and Foulley.

In Chapter 5, a first attempt is made to assess the quality of IRREML by simulation. Simulated data was based on a practical problem involving carcass classification of cattle. For this problem, observations analysed were proportions of agreement between classifiers. Although the data set was large and highly unbalanced, a GLMM with four components of

variance and an over-dispersion parameter could be fitted without problems. The simulation study included various procedures for the construction of confidence intervals and significance tests. These procedures, which were originally derived for LMMs under normality, were applied to the adjusted dependent variate in the last iteration step of IRREML. IRREML and the modified LMM procedures performed satisfactorily.

In Chapter 6, the analysis of threshold models for binary and binomial data is considered. These threshold models are part of the class of GLMMs. A simulation study, mimicking an animal breeding experiment for binary data, indicated that IRREML may perform poorly when the number of observations per random effect is small. In terms of the animal breeding experiment: IRREML estimates of heritability may be considerably biased when the data set consists of a large number of small families. In contrast to other results in the literature, it was found that both under- and overestimation may occur, depending on the relative number of fixed effects in the model. In an animal breeding experiment, fixed effects usually represent a very large number of herds, years and seasons, which are all nuisance parameters, since interest centers on variance components and predicted random effects for animals (representing their genetic merit).

In Chapter 7, IRREML is extended towards threshold models for ordinal data. Estimation includes additional shape parameters for a wide class of underlying distributions. For instance, heterogeneity of residual variances of an underlying normal distribution may be modelled in terms of factors and covariates employing a logarithmic link function.

In Chapter 8, the simulation study for binary data from Chapter 6 is extended and two methods for bias correction of variance component estimators are studied. Minimal dimensions of the data set are identified, such that useful inference about components of variance is feasible.

In Chapter 9, prediction of random effects in a model for normal data with heterogeneous variances is considered. In this model, both means and variances are expressed in terms of fixed and random effects, involving both additive and multiplicative effects. The estimation procedure was developed as a basis for a new national breeding evaluation method for Dutch dairy cattle. It was implemented by the Dutch Cattle Syndicate in Arnhem in 1995. Data sets in the dairy industry are extremely large, and therefore computational aspects were very important. A data set comprising 12,629,403 milk records was analysed. Ideas behind IRREML were used to motivate the estimation procedure. The performance of the procedure was assessed by simulation.

In Chapter 10 the relationship between estimation by IRREML and maximum likelihood (ML) estimation, is discussed in some detail. Employing Laplace integration, IRREML may be shown to be an approximate ML procedure. The poor asymptotic properties of IRREML when the number of binary observations per random effect is limited and the number of random effects is large, are illustrated by a simple over-dispersion model for binomial data. Since ML was seen to perform well, the Gibbs sampler, as a powerful numerical integrator to derive approximate ML estimates, seems a promising technique for datasets of this kind.

## Gegeneraliseerde lineaire modellen met extra stochastische termen en bijbehorende variantiecomponenten (samenvatting)

Dit proefschrift bestaat uit een reeks artikelen die zijn voortgekomen uit een behoefte aan statistische methodologie voor modellen met variantiecomponenten voor niet-normaal verdeelde waarnemingen. Deze methodologie zou algemeen toepasbaar moeten zijn binnen het onderzoek verricht door de instituten verbonden aan de Dienst Landbouwkundig Onderzoek (DLO) van het Ministerie van Landbouw, Natuurbeheer en Visserij, met zo min mogelijk numerieke beperkingen. Beschikbare algorithmen voor het berekenen van "maximum likelihood" (ML) schatters, als gevolg van numerieke beperkingen, maakten slechts analyse van betrekkelijk eenvoudige correlatiestructuren mogelijk. Aanpassing van het iteratieve gewogen kleinste-kwadraten-algorithme (iterative re-weighted least squares, afgekort IRLS), een veelgebruikt algorithme voor gegeneraliseerde lineaire modellen (generalized linear models, afgekort GLMs), leek een veelbelovend alternatief.

De klasse van modellen die in deze dissertatie wordt beschouwd, verder aangeduid als GLMMs (generalized linear mixed models), vormt een directe uitbreiding van de klasse van GLMs. De schattingsprocedure voor GLMMs, verkregen door de kleinste kwadraten methode te vervangen door methodologie voor lineaire gemengde modellen (lineair mixed models, afgekort LMMs), is een directe uitbreiding van het IRLS algorithme voor GLMs. De nieuwe procedure, verder aangeduid als IRREML (iterative re-weighted restricted maximum likelihood), is gebaseerd op iteratief gebruik van restricted maximum likelihood (REML). REML is een schattingsmethode ontwikkeld voor "gewone" LMMs voor normaal verdeelde waarnemingen. Programmatuur voor gebruik van REML is ruimschoots voorhanden. In dit proefschrift is gebruik gemaakt van voorzieningen binnen de statistische programmeertaal Genstat 5 (het standaard statistisch pakket binnen DLO). In elke iteratiestap van IRREML, wordt REML toegepast binnen een benaderend LMM voor een nieuwe afhankelijke variabele. Deze variabele en bijbehorende residuele gewichten, die de "adjusted dependent variate" en de "iterative weights" worden genoemd (waarbij we vasthouden aan de GLM terminologie voor overeénkomende grootheden in het IRLS algorithme), worden na ieder iteratieslag opnieuw berekend. Numerieke beperkingen zijn dezelfde als voor REML in LMMs voor normaal verdeelde waarnemingen en hebben betrekking op de omvang van matrices die moeten worden geïnverteerd. Deze beperkingen kunnen in belangrijke mate worden weggenomen door gebruik te maken van zogenaamde absorptietechnieken, wat neer komt op eliminatie van effecten behorende bij een factor met een groot aantal niveaus. De schattingsprocedure, geprogrammeerd in Genstat 5, is beschikbaar via de Genstat 5 procedurebibliotheek van de Groep Landbouwwiskunde (GLW-DLO) en is inmiddels veelvuldig binnen en buiten de DLO instituten gebruikt.

Na de introductie in hoofdstuk 1, volgt in hoofdstukken 2 en 3 een discussie van LMMs voor normale data, met de nadruk op REML, en van over- en ondergedisperseerde GLMs,

met een illustratie van het schatten van parameters met behulp van de maximum quasi-likelihood methode.

IRREML wordt geïntroduceerd in hoofdstuk 4. Zoals blijkt uit de discussie in dit hoofdstuk, is de schattingsmethode onafhankelijk ontwikkeld door een aantal statistici, vanuit verschillende uitgangspunten, maar resulterend in dezelfde schattingsvergelijkingen. In een Bayesiaanse context is een predictiemethode voor de stochastische effecten in modellen voor binomiale gegevens en ordinale gegevens al in 1983 voorgesteld door Daniel Gianola en Jean-Louis Foulley. Deze methode geeft dezelfde predicties als IRREML.

In hoofdstuk 5 wordt een eerste aanzet gegeven tot validatie van de schattingmethode op basis van simulatieresultaten. De simulatie is gebaseerd op een praktijkprobleem betreffende klassificatie van runderkarkassen. De waarnemingen werden geanalyseerd als fracties die de mate van overeenstemming tussen klassificateurs weergeven. Ofschoon de dataset omvangrijk en zeer ongebalanceerd was, kon een GLMM met vier variantiecomponenten en een overdispersieparameter zonder problemen aan de data worden aangepast. In de simulatie werden ook verschillende procedures voor de constructie van betrouwbaarheidsintervallen en significantietoetsen meegenomen. Deze procedures, die oorspronkelijk zijn ontwikkeld voor LMMs, zijn toegepast binnen het benaderende LMM voor de nieuwe afhankelijke variabele in de laatste iteratiestap. IRREML en de (aangepaste) procedures voor LMMs blijken goed te presteren.

In hoofdstuk 6 worden drempelmodellen voor 0-1 gegevens en binomiale waarnemingen beschouwd. Deze drempelmodellen behoren tot de klasse van GLMMs. Uit de resultaten van een simulatiestudie, waarin een fokkerij experiment voor 0-1 gegevens wordt nagebootst, blijkt dat IRREML slecht presteert wanneer het aantal waarnemingen per stochastisch effect gering is. In termen van het fokkerijexperiment: IRREML-schattingen voor variantiecomponenten en erflijkheidsgraden kunnen zeer onzuiver zijn wanneer de gegevens afkomstig zijn van een groot aantal kleine families. In tegenstelling tot andere simulatieresultaten uit de literatuur blijkt dat zowel onderschatting als overschatting van de variantiecomponenten kan optreden. Dit hangt samen met het aantal vaste effecten in het model. In modellen gehanteerd binnen de fokkerij representeren vaste effecten een doorgaans groot aantal bedrijfs-, jaar- en seizoenseffecten, waarbij de interesse uitgaat naar de variantiecomponenten en voorspellingen voor de stochastische diereffecten (welke het genetisch potentiëel van de dieren vertegenwoordigen).

In hoofdstuk 7 wordt IRREML uitgebreid zodat ook drempelmodellen voor ordinale data kunnen worden geanalyseerd. Vormparameters voor een breed scala van onderliggende verdelingen kunnen ook worden geschat. Zo is het bijvoorbeeld mogelijk heterogene restvarianties van onderliggende normale verdelingen op log-schaal te modelleren in termen van factoren en verklarende variabelen.

In hoofdstuk 8 wordt de simulatiestudie uit hoofdstuk 6 uitgebreid. Twee methoden voor correctie voor onzuiverheid worden bestudeerd. De minimale omvang van een dataset, die betrouwbare conclusies omtrent variantiecomponenten toelaat, wordt aangegeven.

In hoofdstuk 9 wordt de voorspelling van stochastische effecten in een model voor normaal verdeelde gegevens met heterogene variantiestructuur besproken. In het model worden zowel verwachtingswaarden als varianties weergegeven als functie van vaste en stochastische effecten, waarbij zowel additieve als multiplicatieve effecten een rol spelen. De schattingsmethode is ontwikkeld als basis voor een nieuwe nationale methode voor het berekenen van fokwaarden voor melkproductie en door het Nederlands Rundvee Syndicaat te Arnhem in 1995 geïmplementeerd en in gebruik genomen. Datasets betreffende melkopbrengst zijn zeer groot en numerieke aspecten spelen een overheersende rol. Een dataset met 12629403 melkproductiegegevens werd met de nieuwe methode geanalyseerd. Ideeën achter IRREML vormden de basis voor de voorspellingsmethode. Uit simulatie-resultaten werd een gunstige indruk verkregen omtrent de kwaliteiten van de methode.

In hoofdstuk 10 wordt de samenhang tussen IRREML en ML schatters, in meer detail dan in enkele van de voorafgaande hoofdstukken het geval is, beschreven. Met behulp van Laplace-integratie kan IRREML als een benaderende ML methode worden afgeleid. De magere prestaties van IRREML, wanneer het aantal 0-1 gegevens per stochastisch effect gering is, worden aan de hand van een eenvoudig overdispersiemodel voor binomiale gegevens geïllustreerd. Daar de ML methode wel goed presteert, kan worden geconcludeerd dat Gibbs-sampling, als een krachtige numerieke integrator voor een benaderende ML oplossing, voor deze situatie een veelbelovende aanpak is. Daarbij moet worden aangetekend dat Gibbs-sampling een reken- en ervaringsintensieve methode is, met eigen lastige problemen, zoals (trage) convergentie, afhankelijke trekkingen uit de posterior verdeling en gevolgen van de keuze van (niet-informatieve) a priori verdelingen.

# Curriculum vitae

Bastiaan Engel werd op 3 februari 1955 in Oostzaan geboren. In 1972 behaalde hij aan het Zaanlands Lyceum te Zaandam het HBS-B diploma. Aansluitend studeerde hij aan de Universiteit van Amsterdam wis- en natuurkunde. In 1980 werd cum laude het doctoraal examen wiskunde met hoofdvakken mathematische statistiek en kansrekening en bijvak besliskunde bij Prof. Dr. J. Hemelrijk afgelegd. Tijdens de doctoraalfase werd tevens de eerstegraads onderwijsbevoegdheid voor wiskunde behaald en was de auteur van dit proefschrift gedurende twee jaar als kandidaatsassistent betrokken bij het statistiekonderwijs aan kandidaats- en doctoraalstudenten. In 1980 trad de auteur in dienst bij TNO, waar hij achtereenvolgens bij het Instituut voor Informatieverwerking en Statistiek (IWIS-TNO) in Den Haag en bij het Instituut voor Toegepaste Informatica (ITI-TNO) in Delft als statisticus werkzaam was. In 1982 stelde TNO hem in de gelegenheid een jaar lang een post-graduate opleiding aan de Universiteit van Kent te Canterbury te volgen, waar de graad "Master of Science in Statistics" werd behaald. In 1987 werden de biometrisch georiënteerde statistici, waaronder de auteur, uit TNO gelicht en als Groep Landbouwwiskunde (GLW-DLO) aan de Dienst Landbouwkundig Onderzoek (DLO) van het Ministerie van Landbouw Natuurbeheer en Visserij in Wageningen toegevoegd. De inhoud van dit proefschrift is ontstaan uit een behoefte aan gemengde modellen voor niet-normaal verdeelde waarnemingen voor het onderzoek binnen de DLO-instituten. Het onderzoek is uitgevoerd binnen het onderzoeksprogramma van GLW-DLO als onderdeel van de concerntaken voor DLO. De bijbehorende algorithmes zijn door collega GLW-statisticus Bertus Keen beschikbaar gemaakt voor gebruikers van de statistische programmeertaal Genstat 5 (standaard binnen DLO) en zijn inmiddels vele malen zowel binnen als buiten DLO met vrucht toegepast. De resultaten zijn op congressen en workshops in binnen- en buitenland gepresenteerd. De auteur werd ondermeer geïnviteerd als lid van de programmacommissie voor het zevende Symposium voor Statistische Software te Utrecht en als eerste discussiant voor een bijeenkomst van de Royal Statistical Society te Londen en was "invited speaker" op het 40e Biometrisches Kolloquium te Münster, de XIIIe International Biometric Conference te Amsterdam en de najaarsbijeenkomst van de Danish Society for Theoretical Statistics te Århus in 1996.