Efficient and Robust Estimation for a Class of Generalized Linear Longitudinal Mixed Models

René Holst
rho@aqua.dtu.dk
National Institute of Aquatic Resources
Technical University of Denmark
Box 101, DK-9850 Hirtshals, Denmark

and

Bent Jørgensen
bentj@stat.sdu.dk
Department of Statistics
University of Southern Denmark
Campusvej 55, DK-5230 Odense M, Denmark
Abstract
We propose a versatile and computationally efficient estimating equation method for a class of hierarchical multiplicative generalized linear mixed models with additive dispersion components, based on explicit modelling of the covariance structure. The class combines longitudinal and random effects models and retains a marginal as well as a conditional interpretation. The estimation procedure combines that of generalized estimating equations for the regression with residual maximum likelihood estimation for the association parameters. This avoids the multidimensional integral of the conventional generalized linear mixed models likelihood and allows an extension of the robust empirical sandwich estimator for use with both association and regression parameters. The method is applied to a set of otolith data, used for age determination of fish.

Key words: Bias correction; Best linear unbiased predictor; Crowder weights; Dispersion components; Generalized estimating equation; Nuisance parameter insensitivity; Pearson estimating function; Residual maximum likelihood; Tweedie distribution.

1 Introduction

Ever since Nelder and Wedderburn (1972) introduced generalized linear models for independent data, there has been a steady development of methods for analysis of non-normal correlated data. This development was accelerated by the introduction of generalized estimating equations (Liang and Zeger, 1986) and generalized linear mixed models (Schall, 1991; Breslow and Clayton, 1993; Wolfinger and O'Connell, 1993). These two types of models differ conceptually and computationally as reflected in the conventional distinction between marginal and conditional models.

In practice, however, one is often faced with a combination of longitudinal and random effects, where neither of the two, on their own, are adequate. In this light, it is somewhat of an enigma why generalized estimating equations and generalized linear mixed models have continued to evolve along separate paths. With few exceptions (McCulloch and Searle, 2001; Diggle et al., 2002; Fitzmaurice et al., 2004), the literature is clearly divided into two separate strands. Pinheiro and Bates (2000) combined the two approaches for normal data. Ziegler et al. (1998) and Hall (2001) summarized the first decade of developments for generalized estimating equations and recent contributions include for example Hardin and Hilbe (2003), Wang and Carey (2004), Coull et al. (2006) and Wang and Hanfelt (2007). For generalized linear mixed models, we refer to recent monographs, such as Verbeke and Molenberghs (2000), Lee et al. (2006) and references therein.

In the present paper we propose a versatile and computationally efficient method for generalized linear longitudinal mixed models. The estimating equations used for the regression parameters are similar in style to those known from conventional generalized estimating equations, whereas Pearson estimating equations are used for the association parameters. The method combines
longitudinal and random effects models while retaining a marginal as well as a conditional interpretation. A serial correlation structure is employed within clusters, but unlike the state space models of Jørgensen et al. (1999) and Jørgensen and Song (2007), where the latent process is non-stationary, our approach is based on a stationary latent process defined by means of a linear filter.

In order to avoid the intricate efficiency considerations associated with conventional generalized estimating equations, see eg. Wang and Hanfelt (2003), we emphasize explicit modelling of the covariance structure based on second-moment assumptions for the data-generating process. An example of the utility of this approach is the twin data analysis by Iachina et al. (2002), where the correlation between the two twins in a pair was estimated on the basis of a generalized estimating equations model. Nevertheless, the method allows the use of a working correlation structure and we extend the robust empirical sandwich estimator to handle the asymptotic variance for both regression and association parameters.

Our estimation of the association parameters compares to that of residual maximum likelihood by means of the bias-corrected Pearson estimating equations of Jørgensen and Knudsen (2004), following earlier work by McCullagh and Tibshirani (1990) and Hall and Severini (1998).

The estimating equations are solved by an efficient Newton scoring algorithm, thereby circumventing the problems associated with the multidimensional integral defining the likelihood in conventional generalized linear mixed models approaches such as Schall (1991), Breslow and Clayton (1993) and Wolfinger and O’Connell (1993).

The models covered by our approach are defined hierarchically via conditional Tweedie distributions, much like the multiplicative mixed effects models of Ma and Jørgensen (2007) and Ma et al. (2009). This leads to a multiplicative mean structure with a corresponding additive decomposition of the variance into dispersion components, thereby retaining much of the simplicity of classical linear models. The Tweedie family provides a flexible class of models for both positive continuous data, count data and positive continuous data with a point mass at zero (Jørgensen, 1997, Ch. 4), see also Jørgensen and Song (2007).

### 2 Model

#### 2.1 Model specification

We now introduce the main type of our approach followed by a discussion of their covariance structure, which is crucial for the interpretation and estimation of the models. The model is based on the class of Tweedie exponential dispersion models (Jørgensen, 1997, Ch. 4). A Tweedie variable \( Y \sim Tw_r(\mu, \sigma^2) \) is characterized by having \( E(Y) = \mu \) and \( \text{var}(Y) = \sigma^2 \mu^r \). Special cases include the normal \((r = 0)\), Poisson \((r = 1 \text{ and } \sigma^2 = 1)\) and gamma \((r = 2)\) families. The case \( 1 < r < 2 \) correspond to compound Poisson distributions, which are non-negative and continuous, except for a positive probability at zero.
For a given cluster \( i \) and time \( t \) consider a response vector \( Y_{it} \) with conditionally independent Tweedie distributions. For ease of presentation we consider a balanced design with \( T \) equidistant observation times common to all \( I \) clusters. The model is readily adapted to ragged structures.

The cluster random effect is represented by independent latent Tweedie variables,

\[
Z_i \sim Tw_{r_1}(1, \sigma^2),
\]

where \( r_1 \geq 2 \) in order to make \( Z_i \) positive. Given the cluster variable \( Z_i \), we consider a latent process based on Tweedie noise,

\[
Z_{it} \mid Z_i = z_i \sim Tw_{r_2}(\alpha^{-1} z_i, \alpha^{r_2} \omega^2 z_i^{1-r_2}),
\]

where \( r_2 \geq 2 \). Here \( \alpha = \sum_{k=0}^{\infty} \alpha_k < \infty \) with \( \alpha_0 = 1 \) and \( \alpha_k \in [0, 1) \) for \( k > 0 \). The coefficients \( \alpha_k \) determine a conditionally weakly stationary latent process \( Q_{it} \), defined by the linear filter

\[
Q_{it} = \sum_{s=0}^{\infty} \alpha_s Z_{i t-s}.
\]

By way of construction of the middle layer of the latent process \( Q_{it} \) has mean 1. At the observation level we assume

\[
Y_{itj} \mid Q_{is} = q_{is} \sim Tw_{r_3}(\mu_{it} q_{it}, \rho^2 q_{it}^{1-r_3}),
\]

with conditional independence given \( Q_{is} \). Here the * notation denotes the vector obtained by letting the corresponding index run, so that \( Y_{is} = (Y_{i1}, \ldots, Y_{iT})^T \) and so on. By definition of the Tweedie variance function we obtain linearity in the conditioning variable of the mean and variance, so that \( E(Y_{it} \mid Q_{is}) = q_{it} \mu_{it} \) and \( \text{var}(Y_{it} \mid Q_{is}) = q_{it} \rho^2 \mu_{it}^{r_3} \). This property is essential for the derivation of the covariance structure and the estimating functions below. In the Poisson case (\( r_3 = 1 \)) it is convenient to let the dispersion parameter \( \rho^2 > 0 \) accommodate potential over- or under-dispersion.

A variant of the model, applicable to normal response variables, assumes normal zero mean random cluster effects, \( Z_i \sim N(0, \sigma^2) \), replacing (1). The noise process (2) is then assumed to be Gaussian, \( Z_{it} \mid Z_i = z_i \sim N(z_i, \omega^2) \), while maintaining the filter (3) as above. At the response level (4) is replaced by an additive structure with identity link function, \( Y_{it} \mid Q_{is} = q_{is} \sim N(\mu_{it} + q_{it}, \rho^2) \). Since the structure is linear, the corresponding covariance structure is easily derived.

The marginal means may depend on covariates \( \mu_{it} = \mu_{it}(x_{it}; \beta) \), where \( \beta \) denotes a vector of regression parameters. With positive data, the log link is a suitable choice, providing a natural interpretation of the regression parameters. Furthermore the log link, along with the multiplicative structure, enables easy comparison with conventional generalized linear mixed models, where the random effects enter as a term in the linear predictor: \( \eta_{it} = \log(\mu_{it} q_{it}) = x_{it}^T \beta + \log(q_{it}) \).
2.2 Covariance structure

The marginal variance-covariance matrix of the observation vector $Y_{**}$ is crucial for the inference and estimation procedures. Detailed derivations are found in Appendix 1.

The covariance between two given observations within the $i$th cluster is

$$\text{cov} (Y_{it}, Y_{it'}) = \sigma_2 \mu_{it} \mu_{it'} + \omega^2 \mu_{it} \mu_{it'} \sum_{s=0}^{\infty} \alpha_s \alpha_{s+|t-t'|} + \delta_{i}^{t'} \rho^2 \mu_{i}^{r_3},$$

where $\delta_{i}^{t'}$ is the Kronecker delta, being 1 for $i = i'$ and zero otherwise. It is an important property of the model that the covariance does not depend on $r_1$ and $r_2$. From this we now derive a matrix expression for $\text{var} (Y_{**})$.

First we consider the latent process correlation matrix, $K(\alpha)$, with $tt'$th entry $\sum_{s=0}^{\infty} \alpha_s \alpha_{s+|t-t'|}$. Next let $1_T$ denote the $T$-vector of 1s. In matrix notation the variance-covariance matrix of the response vector for the $i$th cluster may then be expressed as

$$\text{var} (Y_{is}) = \mu_{is} \mu_{is}^T \odot \left\{ \sigma_2^2 1_T 1_T^T + \omega^2 K(\alpha) \right\} + \rho^2 \text{diag} (\mu_{i}^{r_3})$$

$$= \sigma_2^2 \mu_{is} \mu_{is}^T + \omega^2 \text{diag} (\mu_{is}) K(\alpha) \text{diag} (\mu_{is}) + \rho^2 \text{diag} (\mu_{i}^{r_3}), \quad (5)$$

say, where $\odot$ is the Hadamard (elementwise) product (Magnus and Neudecker, 1999, p. 45).

Similar to conventional linear mixed models, the variance is decomposed into components of dispersion corresponding to the different sources of variation. The covariance terms in (5) reflect the observation error, the covariance within cluster and the variation between clusters.

The models, accommodated by our approach, hence extend the range of possible serial correlation patterns compared with the conventional generalized estimating equations correlation structures usually considered. Particular covariance structures may be obtained by imposing restrictions on the linear filter parameter vector $\alpha$ or the dispersion parameters. Table lists the more common covariance structures and the corresponding parameter restrictions.

3 Estimation

3.1 General issues

The set of parameters $\theta$ to be estimated is naturally partitioned into regression and association parameters, $\theta = (\beta^T, \gamma^T)^T$, where the regression parameters $\beta$ usually are those of interest whereas the association parameters $\gamma$, containing dispersion and correlation parameters, are often considered nuisance parameters. For estimation of the parameters we use a set of corresponding estimating functions denoted $\psi = (\psi_\beta^T, \psi_\gamma^T)^T$.

The estimating function for the regression parameters is

$$\psi_\beta = \sum_{i=1}^{I} D_i^T C_i^{-1} (Y_i - E(Y_i)), \quad (6)$$
Table 1: Standard covariance structures. The \text{MA}(p)\text{-type} and \text{AR}(p)\text{-type} refer to the latent process correlation structure conditionally on the cluster random effects.

| Covariance structure | Parameter restrictions |
|----------------------|------------------------|
| Independent          | $\omega_j^2 = \sigma^2 = 0$. |
| Exchangeable         | $\omega_j^2 = \rho_j^2 = 0$ and $\alpha_s = 0$ for $s > 0$. |
| \text{MA}(p)\text{-type} | $\alpha_s = 0$ for $s > p$. |
| \text{AR}(p)\text{-type} | For $p = 1$ $\alpha_s = \alpha^s$. For $p > 1$ the $\alpha_s$ are given by the Yule-Walker equations. |
| GLMM                 | $\omega_j^2 = 0$ and $\alpha_s = 0$ for $s > 0$. |

where $D_i = \nabla \beta \mathbb{E}(Y_i) = \partial \mathbb{E}(Y_i)/\partial \beta^T$ and $C_i = \text{var}(Y_i)$. Although (6) is similar to the well known estimating function for the regression parameters from the conventional generalized estimating equations framework (Liang and Zeger, 1986), it corresponds to using the model covariance matrix (5) rather than the working covariance matrix. The conventional generalized estimating equations working covariance matrix is built around the working correlation matrix $R(\alpha)$ so that

$$\text{var}(Y_i) = \phi A_i^{1/2}(\mu_i) R(\alpha) A_i^{1/2}(\mu_i),$$

where $\phi$ is a dispersion parameter, $A_i(\mu_i) = \text{diag}\{v(\mu_{is})\}$ and $v(\cdot)$ is the variance function. In contrast, we emphasize the decomposition of the variance into components of dispersion and associate the process correlation matrix $K(\alpha)$ with an appropriate level in the hierarchy.

We use Pearson estimating functions for the estimation of the association parameters $\gamma = (\gamma_1, \ldots, \gamma_N)^T$. The entire vector of functions is denoted $\psi_\gamma = (\psi_{\gamma_1}, \ldots, \psi_{\gamma_N})^T$, where $N = 3 + M$ and $M = \text{dim}(\alpha)$ and with the $n$th component given by

$$\psi_{\gamma_n}(\beta, \gamma) = \sum_{i=1}^I \text{tr} \{W_{in} (r_i r_i^T - C_i)\},$$

where $r_i = Y_i - E(Y_i)$ and $W_{in}$ are suitable weights. This form emphasizes the model covariance matrix in contrast to the more conventional expressions of the Pearson estimating function (Jørgensen and Knudsen, 2004).

The estimating functions $\psi_\beta$ and $\psi_\gamma$ are explained in more detail below, in Section 3.4 and 3.5 respectively.

3.2 Sensitivity

Cox and Reid (1987) studied parameter orthogonality in the likelihood framework corresponding to block diagonality of the Fisher information matrix. Jørgensen and Knudsen (2004) studied the corresponding property of
nuisance parameter insensitivity in an estimating equation context, by means
of the sensitivity matrix, defined by $S_{\theta} = E \{ \nabla_{\theta} \psi(\theta) \}$, where $\nabla$ is the gradient operator. The sensitivity matrix may be partitioned into blocks corresponding to $(\psi_{\beta}^T, \psi_{\gamma}^T)^T$ and $(\beta^T, \gamma^T)$ as follows:

$$S_{\theta} = \begin{bmatrix} S_{\beta}(\theta) & S_{\beta\gamma}(\theta) \\ S_{\gamma\beta}(\theta) & S_{\gamma}(\theta) \end{bmatrix} = \begin{bmatrix} E \{ \nabla_{\beta} \psi_{\beta}(\beta, \gamma) \} & E \{ \nabla_{\gamma} \psi_{\beta}(\beta, \gamma) \} \\ E \{ \nabla_{\beta} \psi_{\gamma}(\beta, \gamma) \} & E \{ \nabla_{\gamma} \psi_{\gamma}(\beta, \gamma) \} \end{bmatrix}.$$  

Nuisance parameter insensitivity (for short denoted $\gamma$-insensitivity) is defined by the upper right-hand block $S_{\beta\gamma}(\theta)$ being zero. First of all this implies efficiency stable estimation of $\beta$, meaning that the estimation of $\gamma$ does not affect the asymptotic variance of $\hat{\beta}$; see Section 3.7. Second, it simplifies the Newton scoring algorithm (Jørgensen and Knudsen, 2004) as detailed below. Third, it implies that $\hat{\beta}_{\gamma}$ varies only slowly with $\gamma$, where $\hat{\beta}_{\gamma}$ is the estimate of $\beta$ for with $\gamma$ known. While nuisance parameter-insensitivity does not ensure asymptotic independence of $\hat{\beta}$ and $\hat{\gamma}$, it does ease the computation of the asymptotic variance of $\hat{\beta}$.

Following Jørgensen and Knudsen (2004) it is easily seen that $\psi_{\beta}$ is $\gamma$-insensitive. In fact, from (6) we see that $\psi_{\beta}$ depends on $\gamma$ only via $C_i^{-1}$ and hence $\nabla_{\gamma} \psi_{\beta}(\beta, \gamma)$ has zero mean, i.e. $S_{\beta\gamma}(\theta) = 0$.

In the rest of the paper we write $S_{\beta}$ for $S_{\beta}(\theta)$ etc, whenever the meaning is unambiguous. The remaining blocks of $S_{\theta}$ are detailed along with the estimating functions in Sections 3.4 and 3.5.

### 3.3 Algorithm

Calculation of the parameter estimates is achieved by the Newton scoring algorithm (Jørgensen et al., 1996) in which we update the previous value of $\theta$ by

$$\theta^* = \theta - S_{\theta}^{-1} \psi(\theta).$$

By the regularity of $\psi$, the $\gamma$-insensitivity of $\psi_{\beta}$, and using simple matrix manipulations we may express the inverse of $S_{\theta}$ in blocks as follows:

$$S_{\theta}^{-1} = \begin{bmatrix} S_{\beta}^{-1} & 0 \\ -S_{\gamma}^{-1}S_{\beta}S_{\gamma}^{-1} & S_{\gamma}^{-1} \end{bmatrix}. \quad (8)$$

The algorithm therefore splits into a $\beta$ step

$$\beta^* = \beta - S_{\beta}^{-1} \psi_{\beta}(\theta) \quad (9)$$

and a $\gamma$ step

$$\gamma^* = \gamma + S_{\gamma}^{-1}S_{\beta}S_{\gamma}^{-1} \psi_{\beta}(\theta) - S_{\gamma}^{-1} \psi_{\gamma}(\theta)$$

$$= \gamma - S_{\gamma}^{-1} \left\{ \psi_{\gamma}(\theta) - S_{\gamma}^{-1}S_{\beta} \psi_{\beta}(\theta) \right\}. \quad (10)$$

Following Jørgensen and Knudsen (2004) we insert $\beta^*$ from (9) into equation (10). Since equation (9) can be rewritten as $-S_{\beta}^{-1}(\theta) \psi_{\beta}(\theta) = \beta^* - \beta$, this
makes \( S^{-1}_\beta (\theta^*) \psi_\beta (\theta^*) = 0 \), where \( \theta^* \) indicates \( \beta^* \) is being used. Consequently the modified \( \gamma \) step becomes
\[
\gamma^* = \gamma - S^{-1}_\gamma \psi_\gamma (\theta^*). \tag{11}
\]

Analogously we use the most recent estimate of \( \gamma \) when updating \( \beta \) in (9). This is however of less importance, due to the slow variation of \( \hat{\beta}_\gamma \) with \( \gamma \).

### 3.4 Regression parameters \( \beta \)

Following Ma (1999), Ma et al. (2003) and Ma and Jørgensen (2007) we use best linear unbiased predictor for predicting the random effects. The best linear unbiased predictor of a random variable \( Q \) given the observed data \( Y \) is defined by (Henderson, 1975; Ma, 1999)
\[
\hat{Q} = E (Q) + \text{cov} (Q, Y) \frac{1}{\text{var} (Y)} \{ Y - E (Y) \}. \tag{12}
\]

The model specification using Tweedie distributions allows for derivation of the joint score function \( u (\theta; Y, Q) \) (Ma and Jørgensen 2007). We define unbiased estimating functions \( \psi_\beta \) by substituting the random effects by their respective best linear unbiased predictors, i.e.
\[
\psi_\beta (\theta; Y) = u (\theta; Y, \hat{Q}).
\]

It follows from (12) and the linearity of \( E (\cdot) \) and \( \text{cov} (\cdot, Y) \) that the best linear unbiased predictor of \( AQ + BY \) given \( Y \) is \( A\hat{Q} + BY \), where \( A \) and \( B \) are matrices of suitable dimensions. Since \( u \) is linear in both the observed and the latent variables, \( Y \) and \( Q \), we find that \( \psi_\beta \) is the best linear unbiased predictor of the score function \( u \) given the data. By (12) we therefore arrive at the conventional generalized estimating equations form expression (6)
\[
\psi_\beta = E (u) + \text{cov} (u, Y) C^{-1} \{ Y - E (Y) \} = \sum_{i=1}^{l} \frac{D_i^T C_i^{-1}}{D_i} \{ Y_i - E (Y_i) \}. \tag{13}
\]

Here we have used the independence between clusters, along with the following Bartlett-type identity
\[
D = \nabla_\beta E (Y) = E (Y \cdot u) = \text{cov} (Y, u).
\]

From (6) we furthermore obtain the sensitivity \( S_\beta = E (\nabla_\beta \psi_\beta) \) and variability \( V_\beta = \text{var} (\psi_\beta) \) as
\[
S_\beta = -D^T C^{-1} D, \quad V_\beta = D^T C^{-1} D. \tag{14}
\]

The identity \( V_\beta = -S_\beta \) is characteristic for quasi-score functions. We therefore conclude that \( \psi_\beta \) is optimal within the class of linear estimating functions. This also follows from (13) as the best linear unbiased predictor is optimal among all linear predictors.
3.5 Association parameters $\gamma$

Our approach is akin to that of [Ma and Jørgensen (2007)], but deviates by allowing for correlation structures within clusters. Furthermore Ma and Jørgensen used a closed form ad-hoc estimator for the association parameters. Our estimation of $\gamma$ is based on Pearson estimating functions, following the path of [Hall and Severini (1998)] and [Jørgensen and Knudsen (2004)]. For $\gamma_n$ it is defined by

$$
\psi_{\gamma_n}(\beta, \gamma) = \sum_{i=1}^{I} \left\{ r_i^T W_{in} r_i - \text{tr}(W_{in} C_i) \right\}
$$

where $r_i = Y_i - E(Y_i)$ and $W_{in}$ are suitable weights. By linearity of $E(\cdot)$ and $\text{tr}(\cdot)$ these estimating functions are clearly unbiased since $E(r_i r_i^T) = C_i$.

In the conventional generalized estimating equations framework the Pearson estimating function hinges the estimation of association parameters on a working correlation matrix used for defining $\text{var}(Y_i)$ as shown in (7). In contrast, we emphasize the decomposition of the variance into components of dispersion and associates the process correlation matrix $K(\alpha)$ with an appropriate level in the hierarchy.

For $W_{in}$ we use the weights proposed by [Hall and Severini (1998)],

$$
W_{in} = -\frac{\partial C_i^{-1}}{\partial \gamma_n} = C_i^{-1} \frac{\partial C_i}{\partial \gamma_n} C_i^{-1}.
$$

In the normal case these weights lead to quasi-score functions and in general they provide estimating functions that resemble the structure of the estimating functions (6) for the regression parameters.

From (15) we may derive the $\theta_m$-sensitivity of $\psi_{\gamma_n}$, namely

$$
E \left( \frac{\partial}{\partial \theta_m} \psi_{\gamma_n} \right) = E \left[ \frac{\partial}{\partial \theta_m} \sum_{i=1}^{I} \text{tr} \left\{ W_{in} (r_i r_i^T - C_i) \right\} \right]
$$

$$
= \sum_{i=1}^{I} \text{tr} \left[ W_{in} E \left\{ \frac{\partial}{\partial \theta_m} (r_i r_i^T - C_i) \right\} \right]
$$

$$
= -\sum_{i=1}^{I} \text{tr} \left( W_{in} \frac{\partial C_i}{\partial \theta_m} \right).
$$

Here we have used that the derivatives of $r_i$ do not depend on data so $E \left\{ (\partial r_i/\partial \theta_m) r_i^T \right\} = E \left\{ r_i (\partial r_i^T/\partial \theta_m) \right\} = 0.$
The symmetry between the blocks $S_\gamma$ and $S_{\gamma\beta}$ is highlighted by the forms of the $nm$th entries

$$\{S_\gamma\}_{nm} = - \sum_{i=1}^{I} \text{tr} \left( C_i^{-1} \frac{\partial C_i}{\partial \gamma_n} C_i^{-1} \frac{\partial C_i}{\partial \gamma_m} \right)$$

and

$$\{S_{\gamma\beta}\}_{nm} = - \sum_{i=1}^{I} \text{tr} \left( C_i^{-1} \frac{\partial C_i}{\partial \gamma_n} C_i^{-1} \frac{\partial C_i}{\partial \beta_m} \right)$$

respectively.

### 3.6 Bias correction

The estimation of nuisance parameters may be subject to bias (McCullagh and Tibshirani 1990; Jørgensen and Knudsen 2004), caused by not taking into account the degrees of freedom spent on estimating the regression parameters.

In the spirit of Godambe (1960), Heyde (1997) and Jørgensen and Knudsen (2004) we adjust the estimating function for bias rather than the estimate. The corrected estimating function for $\gamma_n$ becomes

$$\tilde{\psi}_n(\beta, \gamma) = \psi_n(\beta, \gamma) + b_n(\beta, \gamma)$$

$$= \sum_{i=1}^{I} \text{tr} \left\{ W_{in} \left( r_i r_i^T - C_i \right) \right\} + \text{tr} \left\{ \left( \sum_{i=1}^{I} D_i^T W_{in} D_i \right) \left( \sum_{i=1}^{I} D_i^T C_i^{-1} D_i \right)^{-1} \right\}$$

$$= \sum_{i=1}^{I} \text{tr} \left\{ W_{in} \left( r_i r_i^T - C_i \right) \right\} - \text{tr} \left( J^{(\gamma_n)} \beta J^{-1} \beta \right),$$

where $J^{(\gamma_n)} = \partial J/\partial \gamma_n$. The Godambe information $J_\beta$, see Section 3.7, plays a role in the estimating equation context analogous to that of the Fisher information in the likelihood framework, with $J_\beta^{-1}$ being the asymptotic variance of $\hat{\beta}$. The penalty term $b_n(\beta, \gamma)$ therefore represents the $\gamma$-dependency of $J_\beta$, weighted by the precision of the estimate $\hat{\beta}$. In this way it corrects for the effect upon $\psi_\gamma(\hat{\beta}, \gamma)$ of using $\hat{\beta}$.

We note that $b_n(\beta, \gamma) = \partial \log \left| \left| J_\beta^{-1} \right| \right| / \partial \gamma_n$, which may be a more convenient form in some applications.

Since $b_n(\beta, \gamma)$ does not depend on the data, we obtain the $\gamma$- and $\beta$-sensitivity of $\tilde{\psi}_n(\beta, \gamma)$ by amending $S_\gamma$ and $S_{\gamma\beta}$ respectively, with the $\gamma$- and $\beta$-derivatives, of the penalty term, respectively. For the $nm$th entries we obtain

$$\frac{\partial}{\partial \gamma_m} b_n(\beta, \gamma) = \text{tr} \left( J^{(\gamma_n)}_\beta J^{-1}_\beta J^{(\gamma_m)}_\beta J^{-1}_\beta J^{(\gamma_n, \gamma_m)}_\beta J^{-1}_\beta \right)$$

(18)

and

$$\frac{\partial}{\partial \beta_m} b_n(\beta, \gamma) = \text{tr} \left( J^{(\gamma_n)}_\beta J^{-1}_\beta J^{(\beta_m)}_\beta J^{-1}_\beta J^{(\gamma_n, \beta_m)}_\beta J^{-1}_\beta \right).$$

(19)

The derivatives of $J_\beta$ are listed in Appendix 2.
3.7 Godambe information \( J_\theta \)

For joint inference on \( \theta = (\beta^T, \gamma^T)^T \) we use the asymptotic property, valid under mild regularity conditions

\[
\hat{\theta} \sim N(\theta, J_\theta^{-1}),
\]

where \( J_\theta^{-1} = S_\theta^{-1}V_\theta S_\theta^{-T} \), the inverse Godambe information or the sandwich estimator.

The structure of the "bread" \( S_\theta^{-1} \) in the sandwich estimator is \( \hat{\theta} \), with blocks listed in (14), (16) and (17). The lower blocks, associated with \( \gamma \) are however amended with terms for bias correction as given by (18) and (19).

The "meat" part \( V_\theta \) is the variability of \( \psi_\theta \) and may be structured analogously

\[
V_\theta = \begin{bmatrix} V_\beta & V_{\beta\gamma} \\ V_{\gamma\beta} & V_\gamma \end{bmatrix},
\]

where obviously \( V_{\beta\gamma} = V_{\gamma\beta}^T \).

Using (8) and (20) \( J_\theta^{-1} \) may be written as

\[
J_\theta^{-1} = \begin{bmatrix} J_\beta & J_{\beta\gamma} \\ J_{\gamma\beta} & J_\gamma \end{bmatrix}
\]

\[
= \begin{bmatrix} S_\beta^{-1} & 0 \\ -S_\gamma^{-1}S_\beta S_\beta^{-1} & S_\gamma^{-1} \end{bmatrix} \begin{bmatrix} V_\beta & V_{\beta\gamma} \\ V_{\gamma\beta} & V_\gamma \end{bmatrix} \begin{bmatrix} S_\beta^{-1} & -S_\gamma^{-1}S_\beta^T S_\beta^{-1} \\ 0 & S_\gamma^{-1} \end{bmatrix}
\]

\[
= \begin{bmatrix} S_\beta^{-1}V_\beta S_\beta^{-1} & S_\gamma^{-1}(-V_\beta S_\beta^{-1}S_\beta^T S_\beta^{-1} + V_{\gamma\beta}) S_\gamma^{-1} \\ -S_\gamma^{-1}S_\beta^T (-S_\beta S_\beta^{-1}V_\beta + V_{\gamma\beta} S_\beta^{-1}) S_\gamma^{-1} & S_\gamma^{-1}(L + V_{\gamma\beta}) S_\gamma^{-1} \end{bmatrix}
\]

where \( L = S_{\gamma\beta} S_\beta^{-1}(V_\beta S_\beta^{-1}S_\beta^T S_\beta^{-1} - V_{\gamma\beta} S_\beta^{-1}S_\gamma^{-1}) - V_{\gamma\beta} S_\beta^{-1}S_\gamma^{-1} \).

The upper left block of \( J_\theta^{-1} \) shows that the the asymptotic variance of \( \hat{\beta} \) is unaffected by the estimation of \( \gamma \). On the other hand the quantity \( L \) in the lower right block represents the inflation of the asymptotic variance of \( \hat{\gamma} \) caused by the estimation of \( \beta \). By (14) \( S_\beta = -V_\beta \) and therefore the upper right block of (21) reduces to \( S_\beta^{-1} (S_{\gamma\beta} + V_{\gamma\beta}) S_\gamma^{-1} \). If \( S_{\gamma\beta} + V_{\gamma\beta} = 0 \) then \( S_\theta = -V_\theta \) and \( \psi \) would have been a quasi score. In that sense the \( S_{\gamma\beta} + V_{\gamma\beta} \) measures how much \( \psi_\gamma \) deviates from being quasi-score.

Except for \( V_\beta \), the blocks rely on 3rd and 4th moments. For practical use this seems less tractable and we will instead employ empirical variabilities of \( \tilde{\psi} = (\tilde{\psi}_\beta, \tilde{\psi}_\gamma)^T \), defined by \( \tilde{V}_\theta_{\text{Emp}} = \sum_i \tilde{\psi}_i(\hat{\theta})\tilde{\psi}_i(\hat{\theta})^T \). By plugging in \( \tilde{V}_\theta_{\text{Emp}} \) we obtain the empirical sandwich estimator, \( \tilde{J}_\theta^{-1}_{\text{Emp}} = S_\theta^{-1}\tilde{V}_\theta_{\text{Emp}} S_\theta^{-1} \)

\[
\tilde{J}_\theta^{-1}_{\text{Emp}} = \begin{bmatrix} S_\beta^{-1} \tilde{V}_\beta_{\text{Emp}} S_\beta^{-1} & S_\beta^{-1}(-\tilde{V}_\beta_{\text{Emp}} S_\beta^{-1}S_{\gamma\beta} + \tilde{V}_{\gamma\beta,\text{Emp}}^T) S_\gamma^{-1} \\ S_\gamma^{-1}(-S_{\gamma\beta} S_\beta^{-1} \tilde{V}_\beta_{\text{Emp}} + \tilde{V}_{\gamma\beta,\text{Emp}}) S_\beta^{-1} & S_\gamma^{-1}(\tilde{L} + \tilde{V}_{\gamma\beta,\text{Emp}}) S_\gamma^{-1} \end{bmatrix}
\]
where \( \hat{L} = S_{\gamma\beta}S_{\beta}^{-1} \left( \hat{V}_{\beta,\text{Emp}}S_{\beta}^{-1}S_{\gamma\beta}^T - \hat{V}_{\gamma\beta,\text{Emp}}^T \right) - \hat{V}_{\gamma\beta,\text{Emp}}S_{\beta}^{-1}S_{\gamma\beta}^T. \)

We may replace \( \hat{V}_{\beta,\text{Emp}} \) by \( V_{\beta} = S_{\beta}^{-1} \) to obtain the semi-empirical sandwich estimator

\[
\hat{J}_{\theta,\text{SEM}}^{-1} = \begin{bmatrix}
-S_{\beta}^{-1} & S_{\beta}^{-1} \left( S_{\gamma\beta} + \hat{V}_{\gamma\beta,\text{Emp}} \right) S_{\gamma}^{-1} \\
S_{\gamma}^{-1} \left( S_{\gamma\beta} + \hat{V}_{\gamma\beta,\text{Emp}} \right) S_{\beta}^{-1} & S_{\gamma}^{-1} \left( \bar{L} + \hat{V}_{\gamma,\text{Emp}} \right) S_{\gamma}^{-1}
\end{bmatrix},
\]

where now \( \bar{L} = -S_{\gamma\beta}S_{\beta}^{-1} \left( S_{\gamma\beta}^T + \hat{V}_{\gamma\beta,\text{Emp}}^T \right) - \hat{V}_{\gamma\beta,\text{Emp}}S_{\beta}^{-1}S_{\gamma\beta}^T. \)

The bias correction \( b_{\gamma}(\gamma, \beta) \) applied to \( \psi_{\gamma} \) causes that part of \( \hat{\psi} \) to have a non-zero mean value.

### 4 Simulation

Some key properties of our method were addressed by an extensive simulation study in which 4000 data sets were simulated for each of 36 different configurations specified by combinations of the following Tweedie parameters: \( r_1 \in \{1.5, 2.0, 2.5, 3.0\} \), \( r_2 \in \{1.5, 2.0, 3.0\} \) and \( r_3 \in \{1.0, 1.5, 2.0, 3.0\} \). Table 2 lists the model parameter settings used for the simulations. These settings are repeated across all combination of the latent variables Tweedie parameters \( r_1 \) and \( r_2 \). The data sets were simulated with 15 clusters each, and each cluster consisting of latent AR(1) time series of length 30 and a log-linear regression for the fixed part. The correlation parameter \( \alpha \) and the response dispersion parameter \( \rho^2 \) varied with the response model. Except for the Poisson case, for which we used an intercept of 4.0, all other intercepts and all slopes were identical across scenarios. For other response models than the Poisson, the parameters were chosen to attain similar second moments for the marginal response. The coefficient of variation of the marginal response, based on these settings, ranged from 0.497 (Poisson) to 0.579 (Gamma).

As \( \psi_{\beta} \) is a quasi score estimating function, with well known and optimal properties the simulation study naturally focuses on the estimates of the association parameters.

| Response Model          | Regression | Dispersion | Correlation |
|-------------------------|------------|------------|-------------|
| Distribution            | \( r_3 \) | \( \beta_0 \) | \( \beta_1 \) | \( \sigma^2 \) | \( \omega^2 \) | \( \rho^2 \) | \( \alpha \) |
| Poisson                 | 1.0        | 4.0        | 0.3         | 0.05       | 0.15       | 1.0000      | 0.40        |
| Compound Poisson        | 1.5        | 1.6        | 0.3         | 0.05       | 0.15       | 0.1175      | 0.55        |
| Gamma                   | 2.0        | 1.6        | 0.3         | 0.05       | 0.15       | 0.0850      | 0.50        |
| Inverse Gaussian        | 3.0        | 1.6        | 0.3         | 0.05       | 0.15       | 0.0200      | 0.40        |
Figure 1: Median values of $\hat{\sigma}^2$ for bias-corrected (○) and un-corrected (●) estimation compared with the true value $\sigma^2 = 0.05$ (horizontal line).

**Robustness**

Simulations with varying configurations of $r_1$ and $r_2$ was used for studying the assumed robustness against the lack of knowledge about the Tweedie parameters driving the latent process. Along the same lines we investigated how the model performed across an appropriate range of the Tweedie parameter $r_3$ for the response variable.

Figure 1 shows the median values of estimates of $\sigma^2$, for all combinations of the Tweedie parameter considered. Corresponding plots for $\omega^2$, $\rho^2$ and $\alpha$, not included in the article, show similar patterns across the range of $r_1$ values considered. Also there seems very little difference in the patterns across the range of $r_2$ values for $\hat{\rho}^2$ and $\hat{\alpha}$, whereas $\hat{\sigma}^2$ and $\hat{\omega}^2$ show a markedly higher bias for $r_2 = 3$ than for $r_2 = 1.5, 2$. Our approach hence appear reasonably robust against varying specifications of the latent process. The asymptotic variances of the estimates of the association parameters [22], enables us to compute estimates of coverage probabilities for 95% asymptotic confidence intervals, based on these. These coverage probabilities are listed in Table 3. While the coverages indicate the standard errors of the regression parameters to be precise, the coverages are consistently much too big for the association parameters, indicating overestimation of their standard errors.

**Bias correction**

The magnitude of the nuisance parameter bias correction is assessed by a duplicate analysis of the simulated data sets, except that the second estimation
Table 3: Summary of coverages for 95% confidence intervals across varying configurations.

| Statistic | $\beta_0$ | $\beta_1$ | $\sigma^2$ | $\omega^2$ | $\rho^2$ | $\alpha$ |
|-----------|-----------|-----------|------------|------------|----------|--------|
| 1st Qu.   | 73-54%    | 91-62%    | 99-95%     | 97-55%     | 99-12%   | 98-91% |
| Median    | 92-78%    | 94-29%    | 100-00%    | 98-98%     | 99-44%   | 99-32% |
| 3rd Qu.   | 93-09%    | 94-68%    | 100-00%    | 99-83%     | 99-66%   | 99-85% |

is done without bias correction.

Within the range of configurations considered here, there were generally little bias on the average of the estimated association parameters. Apart from a few minor exceptions, that may well be referred to sampling error, the bias correction pulled the estimates closer to their true values. The bottom level dispersion parameter $\sigma^2$ shows markedly the highest correction.

5 Data Analysis

Knowledge about the growth of fish is important for the assessment of fish biomass. For this purpose, many fisheries management programmes sample otoliths on a regular basis. An otolith is a structure located in the inner ear of fish and is built by deposit of calcium carbonate, protein and a variety of trace elements. It carries information about age and growth patterns, by means of alternating opaque and translucent bands. When viewed in transmitted light, a translucent band represents a low level of deposition of proteins in the calcium carbonate crystal structure corresponding to a period of slow growth \cite{Mosegaard1986}. Sub-seasonal bands, representing daily cycles, can sometimes be identified within the annual bands \cite{Pannella1971}.

The data collected and analysed by Clausen et al. \cite{Clausen2007} contains measurements of daily growth bands of otoliths collected from juvenile herrings \textit{(Clupea harengus)}. The age in days was determined, by counting bands, for each of the sampled specimen and along with the time of sampling they were categorized as being offspring from one of three spawner types: autumn, winter and spring. These are distinct stock components but mix on the nursery and feeding grounds. For stock assessment purposes, it is of interest to be able to discriminate between them. Clausen et al. \cite{Clausen2007} used otolith characteristics for this purpose.

With each fish being a cluster and the sequence of bands within fish giving the longitudinal structure, otoliths measurements are amenable to our framework. We analysed the data from Clausen et al. \cite{Clausen2007} to illustrate the use of our model for this type of data.

For compatibility across the collection of otoliths, the band widths are measured along similar radii on all otoliths. If the band marks are not all clearly identifiable along this transect, two or more adjacent bands are aggregated and the total width of these bands is taken (Fig. 2). The count of bands between
two measurement marks is then based on intermediate band marks identified elsewhere on the otoliths. It is common practice to use the average of such aggregated bands, in place of correct measurements; a feature also found in the present data. To avoid successive values obtained from the same aggregation of bands, it sufficed to sub-sample every 8th value for our analysis.

The sampled fish have different ages and therefore display differences in the lengths of their band width series. To avoid bias caused by data selection, we truncated the sequences of band measurements to the shortest sequence within each spawning category. Furthermore the first 10 bands were left out of the analysis, as their measurements were considered too imprecise.

Two variant models were estimated: one fixing the response Tweedie parameter $r_3 = 2$, corresponding to a gamma distribution and the other one estimating this parameter. Judging from exploratory plots (Fig. 3) of the observed width measurements the fixed part could appropriately be modeled as 2nd order polynomials of the bands and with potential different coefficients for the three seasons: $\text{width} \sim (\text{band} + \text{band}^2) \times \text{season}$ using the log link.

The initial models contained 9 regression parameters. Autumn was chosen as base level for the season factor, to enable a direct comparison between autumn and winter, as these appeared most alike among the three seasons. The models were reduced to final models, with 6 regression parameters, through a succession of Walds test and re-estimations. Based on inspection of the auto-correlation and the partial auto-correlation function for individual otoliths, an AR(1) model was deemed appropriate. Estimates for the parameters of the final models and standard errors are listed in Table 4.

The two regressions are estimated almost exactly the same, whether $r_3$ is estimated or assumed known. This reflects the $\gamma$ insensitivity of $\psi_{\beta}$. From the fit we conclude that autumn and winter differ only by the 1st order term whereas autumn and spring differ by all three terms. The fitted curves from
Figure 3: Width measurements at every 8th band. Thick white line indicates average measurements over otoliths. Top row: observed, bottom row: estimated.

Table 4: Parameter estimates, standard errors (SE) and p-values for both fixed and estimated $r_3$ models. * The $p$-value for $r_3$ applies to the hypothesis $H_0 : r_3 = 2$. aut: autumn; win: winter; spr: spring.

| Parameter                  | Fixed $r_3 = 2$                | Estimated $r_3$ |
|----------------------------|-------------------------------|-----------------|
|                            | Est     | SE     | p-value | Est     | SE     | p-value |
| $\beta_{\text{aut+win}}$  | 0.3118  | 0.0292 | $< 0.0001$ | 0.3113  | 0.0292 | $< 0.0001$ |
| $\beta_{\text{spr}}$      | 1.1304  | 0.0553 | $< 0.0001$ | 1.1288  | 0.0556 | $< 0.0001$ |
| $\beta_{\text{spr:band}}$ | 0.0187  | 0.0016 | $< 0.0001$ | 0.0187  | 0.0016 | $< 0.0001$ |
| $\beta_{\text{win:band}}$ | 0.0032  | 0.0003 | $< 0.0001$ | 0.0032  | 0.0003 | $< 0.0001$ |
| $\beta_{(\text{aut+win}):\text{band}}^2$ | $1.9 \times 10^{-5}$  | $1.4 \times 10^{-6}$ | $< 0.0001$ | $1.9 \times 10^{-5}$ | $1.4 \times 10^{-6}$ | $< 0.0001$ |
| $\beta_{\text{spr:band}}^2$ | $-$0.0001  | 9.9 $\times 10^{-6}$ | 0.0001 | $-$0.0001  | 1.0 $\times 10^{-5}$ | $< 0.0001$ |
| $\sigma^2$                 | 0.0040  | 0.1639 | 0.9807 | 0.0042  | 0.1627 | 0.9796 |
| $\omega^2$                | 0.0277  | 2.6770 | 0.9918 | 0.0275  | 3.4696 | 0.9937 |
| $\rho^2$                  | 0.0153  | 4.1817 | 0.9971 | 0.0115  | 7.0517 | 0.9987 |
| $\alpha$                  | 0.8321  | 0.0823 | $< 0.0001$ | 0.8325  | 6.7673 | 0.9021 |
| $r_3$                     | 2.2700  | 1.7627 | 0.8783* |
the fixed-$r_3$ model are plotted in Fig. 3.

The association parameter estimates were very similar for the two models, but giving quite different standard errors. The rather large standard errors for the dispersion parameter estimates confirms the impression from the simulations in Section 4, that the use of empirical variabilities in the sandwich estimator (22) may lead to standard errors too big to be of any practical use. This seems to be the cost of avoiding the use of higher moments. The standard errors for the correlation parameter $\alpha$ in the fixed-$r_3$ case appears to be more realistic but raises dramatically when $r_3$ is estimated. In that case the standard error for $r_3$ seems moderate. The $\alpha$ parameter applies on the scale of the sub-sampling frequency. A back calculation to a day-to-day serial correlation and assuming the AR(1) model, leads to a value of about 0.97.

6 Discussion

There are a few useful extensions of the method worth mentioning here. It would be straightforward to extend the model to multiple levels of random effects, adding further levels by repeated use of conditional Tweedie distributions. A second useful extension would be to allow regression modelling for the association parameters, along the lines of Davidian and Carroll (1987).

Finally, the model can be easily adapted to handle multivariate data. By use of conditionally independent Poisson response variables, the model can be extended to binomial or categorical data, leading to beta-binomial-like or Dirichlet-multinomial-like models. This topic is addressed in a companion article currently in preparation.

Acknowledgements

The authors thank Rob Fryer for valuable comments on our approach and Lotte Worsøe Clausen and Helge Paulsen for providing us with the otolith data and guidance in understanding them.
Appendix 1

Covariance structure

From the model specification (1)–(4) we derive the marginal covariance between two observations within the $i$th cluster. This is done in three steps by means of the law total of variance. From $E(Z)_i = 1$ and $\text{var}(Z_i) = \sigma^2$ we first get

$$\text{cov}(Z_{it}, Z_{it'}) = E\{\text{cov}(Z_{it}, Z_{it'} | Z_s)\} + \text{cov}(E(Z_{it} | Z_s), E(Z_{it'} | Z_s))$$

$$= \delta_t^i E(\omega^2 Z_i) + \alpha_+^2 \text{var}(Z_i)$$

$$= \delta_t^i \omega^2 + \alpha_+^2 \sigma^2,$$

from which we obtain

$$\text{cov}(Q_{it}, Q_{it'}) = \sum_{s=0}^{\infty} \sum_{s'=0}^{\infty} \alpha_s \alpha_{s'} \text{cov}(Z_{i+s}, Z_{i+s'})$$

$$= \omega^2 \sum_{s=0}^{\infty} \alpha_s \alpha_{s+|t-t'|} + \sigma^2,$$

and finally arrive at

$$\text{cov}(Y_{it}, Y_{it'}) = E\{\text{cov}(Y_{it}, Y_{it'} | Z)\} + \text{cov}\{E(Y_{it} | Z), E(Y_{it'} | Z)\}$$

$$= \delta_t^{it'} \text{var}(Y_{it}) + \mu_{it}\mu_{ij'} \text{cov}(Q_{it}, Q_{it'})$$

$$= \delta_t^{it'} \mu_{it} \rho^2 + \mu_{it}\mu_{it'} \left( \omega^2 \sum_{s=0}^{\infty} \alpha_s \alpha_{s+|t-t'|} + \sigma^2 \right)$$

Appendix 2

Process Correlation Matrix $K(\alpha)$ for ma($q$) and ar(1) processes

The latent process linear filter $Q_{it} = \sum_{s=0}^{\infty} \alpha_s Z_{i+s},$ induces the process correlation matrix $K(\alpha)$, with $tt'\text{th}$ entry $\{ K(\alpha) \}_{tt'} = \sum_{s=0}^{\infty} \alpha_s \alpha_{s+|t-t'|}.$

An MA($q$) process is given by $\alpha_0 = 1$ and $\alpha_s = 0$ for $s > q$ and has first and second derivative matrices with $tt'\text{th}$ entries given by

$$\left\{ \frac{\partial}{\partial \alpha_k} K(\alpha) \right\}_{tt'} = \alpha_{k+|t-t'|} \delta_{k\leq q-|t-t'|} + \alpha_{k-|t-t'|} \delta_{k\geq |t-t'|}$$

and

$$\left\{ \frac{\partial^2}{\partial \alpha_k \partial \alpha_m} K(\alpha) \right\}_{tt'} = \delta_{t'}^{it} \delta_{m}^{it} + \delta_{|t-t'|}^{k-m}$$

respectively. Here $\delta_{t'}^{it}, \delta_{k\leq q-|t-t'|}$ etc. are variant forms of the Kronecker delta with obvious definitions.
An AR(1) process is given by $\alpha_s = \alpha^s$; $\alpha \in (0, 1)$, from which we get the $tt'$th entry of $K(\alpha)\{K(\alpha)\}_{tt'} = \sum_{s=0}^{\infty} \alpha^{2s+|t-t'|} = \sum_{s=0}^{\infty} \alpha^{2s} = \frac{\alpha^{t-t'}}{1-\alpha^2}$.

Consequently the $k$th sub- and super-diagonal of $\frac{\partial}{\partial \alpha} K(\alpha)$ and $\frac{\partial^2}{\partial \alpha^2} K(\alpha)$ have elements

$\frac{\partial}{\partial \alpha} \left( \frac{\alpha^k}{1-\alpha^2} \right) = \frac{(2-k)\alpha^{k+1} + k\alpha^{k-1}}{(1-\alpha^2)^2}$

and

$\frac{\partial^2}{\partial \alpha^2} \left( \frac{\alpha^k}{1-\alpha^2} \right) = \frac{(k^2-5k+6)\alpha^{(k+2)} + (-2k^2+6k+2)\alpha^{k} + (k-1)k\alpha^{(k-2)}}{(1-\alpha^2)^3}$

respectively.

**A Appendix 3**

**Derivatives of $J_\beta$**

The derivatives of $J_\beta$ involved in calculating the $\gamma$- and $\beta$- sensitivities of $\tilde{\psi}_{\gamma}(\beta, \gamma)$ are

$J_{\beta}^{(\gamma_n)} = -\sum_{i=1}^{I} D_i^TW_{in}D_i$

$J_{\beta}^{(\beta_m)} = \sum_{i=1}^{I} D_i^{T(\beta_m)}C_{i}^{-1}D_i + D_i^{T}C_{i}^{-1}D_i^{(\beta_m)} - D_i^{T}C_{i}^{-1}C_{i}^{(\beta_m)}C_{i}^{-1}D_i$

$J_{\beta}^{(\gamma_n, \gamma_n)} = \sum_{i=1}^{I} D_i^{T} \left(W_{in}C_{i}W_{in} + W_{in}C_{i}W_{in} - C_{i}^{(\gamma_n, \gamma_n)}C_{i}^{-1}\right)D_i$

$J_{\beta}^{(\gamma_n, \beta_m)} = -\sum_{i=1}^{I} D_i^{(\beta_m)}W_{in}D_i + D_i^{T}W_{in}D_i^{(\beta_m)} + D_i^{T}W_{in}D_i^{(\beta_m)}D_i$, 

where $W_{in} = -\frac{\partial}{\partial \gamma_n} C_{i}^{-1} = C_{i}^{-1} \left(\frac{\partial}{\partial \gamma_n} C_{i}\right) C_{i}^{-1}$ and $D_i^{(\beta_m)} = \frac{\partial}{\partial \beta_m} D_i$ etc.
References

Breslow, N. E. and Clayton, D. G. (1993). Approximate inference in generalized linear mixed models. *Journal of the American Statistical Association* **88**, 9–25.

Clausen, L. A. W., Bekkevold, D., Hatfield, E. M. C., and Mosegaard, H. (2007). Application and validation of otolith microstructure as a stock identification method in mixed Atlantic herring (Clupea harengus) stocks in the North Sea and western Baltic. *ICES J. Mar. Sci.* **64**, 377–385.

Coull, B. A., Houseman, E. A., and Betensky, R. A. (2006). A computationally tractable multivariate random effects model for clustered binary data. *Biometrika* **93**, 587–599.

Cox, D. R. and Reid, N. (1987). Parameter orthogonality and approximate conditional inference. *Journal of the Royal Statistical Society, Series B* **49**, 1–39.

Davidian, M. and Carroll, R. J. (1987). Variance function estimation. *Journal of the American Statistical Association* **82**, 1079–1091.

Diggle, P. J., Heagerty, P., Liang, K.-Y., and Zeger, S. L. (2002). *Analysis of Longitudinal Data*. Oxford University Press, Oxford, 2nd edition.

Fitzmaurice, G. M., Laird, N. M., and Ware, J. H. (2004). *Applied longitudinal analysis*. Wiley-Interscience, Hoboken, N.J.

Godambe, V. P. (1960). An optimum property of regular maximum likelihood estimation. *Annals of Mathematical Statistic* **31**, 1208–1211.

Hall, D. B. (2001). On the application of extended quasi-likelihood to the clustered data case. *The Canadian Journal of Statistics* **29**, 77–97.

Hall, D. B. and Severini, T. B. (1998). Extended generalized estimating equations for clustered data. *Journal of the American Statistical Association* **93**, 1365–1375.

Hardin, J. W. and Hilbe, J. M. (2003). *Generalized Estimating Equations*. Chapman & Hall/CRC, Boca Raton, FL.

Henderson, C. R. (1975). Best linear unbiased estimation and prediction under a selection model. *Biometrics* **31**, 423–447.

Heyde, C. C. (1997). *Quasi-Likelihood and Its Application: A General Approach to Optimal Parameter Estimation*. Springer Series in Statistics. Springer.

Iachina, M., Jørgensen, B., Christensen, K., and Iachine, I. (2002). Analysis of functional abilities for elderly danish twins using gee models. *Twin Research* **5**, 289–293.
Jørgensen, B. (1997). *The Theory of Dispersion Models.* Chapman & Hall, London.

Jørgensen, B. and Knudsen, S. J. (2004). Parameter orthogonality and bias adjustment for estimating functions. *Scandinavian Journal of Statistics* **31**, 93–114.

Jørgensen, B., Labouriau, R., and Lundbye-Christensen, S. (1996). Linear growth curve analysis based on exponential dispersion models. *Journal of the Royal Statistical Society. Series B* **58**, 573–592.

Jørgensen, B., Lundbye-Christensen, S., Song, P. X.-K., and Sun, L. (1999). A state space model for multivariate longitudinal count data. *Biometrika* **86**, 169–181.

Jørgensen, B. and Song, P.-K. (2007). Stationary state space models for longitudinal data. *Canadian Journal of Statistics* **34**, 1–23.

Lee, Y., Nelder, J. A., and Pawitan, Y. (2006). *Generalized Linear Models with Random Effects: Unified Analysis via H-likelihood.* Chapman and Hall, London.

Liang, K.-Y. and Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika* **73**, 13–22.

Ma, R. (1999). *An orthodox BLUP approach to generalized linear mixed models.* PhD thesis, The University of British Columbia.

Ma, R. and Jørgensen, B. (2007). Nested generalized linear mixed models: an orthodox best linear unbiased predictor approach. *Journal of the Royal Statistical Society: Series B* **69**, 625–641.

Ma, R., Jørgensen, B., and Willms, J. (2009). Clustered binary data with random cluster sizes: A dual poisson modelling approach. *Statist. Mod.* **9**, 137–150.

Ma, R., Krewski, D., and Burnett, R. T. (2003). Random effects cox models: a poisson modelling approach. *Biometrika* **90**, 157–169.

Magnus, J. R. and Neudecker, H. (1999). *Matrix Differential Calculus with Applications in Statistics and Econometrics, 2nd Edition.* John Wiley & Sons, Chichester.

McCullagh, P. and Tibshirani, R. (1990). A simple method for the adjustment of profile likelihoods. *Journal of the Royal Statistical Society B* **52**, 325–344.

McCulloch, C. E. and Searle, S. R. (2001). *Generalized, linear, and mixed models.* Wiley-Interscience, New York.

Mosegaard, H. and Titus, R. (1987). Daily growth rates of otoliths in yolk sac fry of two salmonid species at five different temperatures. In Kallander, S. and Farnholm, B., editors, *The V Congress of European Ichthyology, Stockholm*, pages 221–227. Swedish Museum of Natural History, Stockholm.
Nelder, J. and Wedderburn, R. (1972). Generalized linear models. *Journal of the Royal Statistical Society. Series A* **135**, 370–384.

Pannella, G. (1971). Fish otoliths: Daily growth layers and periodical patterns. *Science* **173**, 1124–1127.

Pinheiro, J. C. and Bates, D. M. (2000). *Mixed-effects models in S and S-PLUS*. Springer, New York.

Schall, R. (1991). Estimation in generalized linear models with random effects. *Biometrika* **78**, 719–727.

Verbeke, G. and Molenberghs, G. (2000). *Linear mixed models for longitudinal data*. New York: Springer.

Wang, M. and Hanfelt, J. J. (2003). Adjusted profile estimating function. *Biometrika* **90**, 845–858.

Wang, M. and Hanfelt, J. J. (2007). Orthogonal locally ancillary estimating functions for matched pair studies and errors in covariates. *Journal of the Royal Statistical Society, Series B* **69**, 411–428.

Wang, Y.-G. and Carey, V. (2004). Unbiased estimating equations from working correlation models for irregularly timed repeated measures. *Journal of the American Statistical Association* **99**, 845–853.

Wolfinger, R. and O’Connell, M. (1993). Generalized linear mixed models a pseudo-likelihood approach. *Journal of Statistical Computation and Simulation* **48**, 233–243.

Ziegler, A., Kastner, C., and Blettner, M. (1998). The generalized estimation equations: An annotated bibliography. *Biometrical Journal* **40**, 115139.