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Regression Analysis of Correlated Ordinal Data Using Orthogonalized Residuals

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Summary

Semi-parametric regression models for the joint estimation of marginal mean and within-cluster pairwise association parameters are used in a variety of settings for population-averaged modeling of multivariate categorical outcomes. Recently, a formulation of alternating logistic regressions based on orthogonalized, marginal residuals has been introduced for correlated binary data. Unlike the original procedure based on conditional residuals, its covariance estimator is invariant to the ordering of observations within clusters. In this article, the orthogonalized residuals method is extended to model correlated ordinal data with a global odds ratio, and shown in a simulation study to be more efficient and less biased with regards to estimating within-cluster association parameters than an existing extension to ordinal data of alternating logistic regressions based on conditional residuals. Orthogonalized residuals are used to estimate a model for three correlated ordinal outcomes measured repeatedly in a longitudinal clinical trial of an intervention to improve recovery of patients' perception of altered sensation following jaw surgery.

Keywords

Clustered data; Generalized estimating equations; Marginal models; Proportional odds; Sensory retraining

1. Introduction

Multivariate ordinal outcomes arise in many biomedical and analytical settings, such as in measuring symptoms of psychiatric or rheumatoid arthritis patients, or patients' self-reported recovery following injury or surgery. One such example is an outcome measured

7. Supplementary Materials

Web appendices referenced in Section 3 along with software and data used in the example are available with this paper at the *Biometrics* website on Wiley Online Library.

on a five point Likert scale, common in questionnaires or surveys (Laerhoven, ZaagLoonen, and Derkx, 2004), with possible responses: “strongly disagree,” “disagree,” “neutral,” “agree,” or “strongly agree.” Although the response is monotonically increasing with higher levels, the distance between levels is not well defined.

In another example, individuals may experience altered sensation in the facial area following orthognathic, or jaw, surgery. In a clinical trial of patients who underwent bilateral sagittal split osteotomy, the trajectory of recovery from altered sensation in a group randomized to receive standard post-surgical treatment was compared to that of a group who performed facial sensory retraining exercises in conjunction with the standard treatment (Phillips et al., 2007). Five ordinal outcomes each with seven categories were examined longitudinally, including oral and facial pain, unusual sensations, numbness, and loss of lip sensitivity. In this case, interest was in whether patient recovery was related to the type of treatment after surgery. Interest can also include the association structure of ordinal outcomes, addressing such questions as (1) are pain and numbness closely related and (2) are multiple responses on the same outcome reliable? This article introduces a new statistical method to jointly model multiple ordinal outcomes. Joint modeling is carried out for the jaw surgery data to illuminate pairwise associations among patient-reported ordinal outcomes, while providing a unified framework for assessment of treatment effect.

There are a number of methods for modeling correlated ordinal or, more generally, multinomial data, including those for marginal models (Prentice and Zhao, 1991; Liang, Zeger, and Qaqish, 1992; Heagerty and Zeger, 1996; Ekholm et al., 2003; Touloumis, Agresti, and Kateri, 2013) and subject-specific hierarchical models (Ezzet and Whitehead, 1991; Agresti and Lang, 1993; Crouchley, 1995). The choice between these two classes of models depends on the research question being investigated. For covariates that do not vary within a subject, such as intervention condition in the jaw surgery study, marginal models are recommended because their regression coefficients have population-averaged interpretations (Neuhaus, Kalbfleisch, and Hauck, 1991; Heagerty, 1999). Particularly, marginal models are appropriate in clinical trials where interest is in average treatment effects.

Marginal regression models for correlated multinomial data are commonly based on likelihood methods (Dale, 1986; Lesafire and Molenberghs, 1991; Molenberghs and Lesafire, 1994; Glonek and McCullagh, 1995; Ekholm, 2003) or estimating equations methods (Clayton, 1992; Gange et al., 1995). In contrast to maximum likelihood methods, generalized estimating equations (GEEs) for marginal modeling of categorical data do not make assumptions about the full joint distributions of multinomial outcomes to estimate model parameters. Touloumis et al. (2013) define a GEE approach for analyzing ordinal and multinomial responses where associations are modeled as nuisance parameters with local odds ratios. Liang et al. (1992) defined a marginal model for both marginal means and within-cluster association parameters for multinomial data using estimating equations based on response vectors and vectors of response cross-products. Second order estimating equations for ordinal data solve simultaneously for mean and association parameters. This method can be computationally burdensome for large clusters, having a matrix of dimension $C_n + C^2 \binom{n}{2}$ to invert, where $C + 1$ is the number of multinomial response levels, and n is the

cluster size. First-order GEE (Liang and Zeger, 1986; Lipsitz, Laird, and Harrington, 1991) are less burdensome computationally for large clusters, and have high efficiency for marginal mean model parameters when outcome correlation is not large. They also give consistent estimation of marginal mean model parameters even when the within-cluster association model has been misspecified.

First-order estimating equations using conditional residuals in a model for the association between clustered outcomes can be moderately efficient in relation to second-order equations with less burden computationally (Lipsitz and Fitzmaurice, 1996). In the case of multivariate binary data, alternating logistics regressions (ALR), which specify within-cluster associations in term of pairwise odds ratios (Carey, Zeger, and Diggle, 1993), have been applied in diverse settings, including studies of multilevel geographical clustering of drug (Petronis and Anthony, 2003) and alcohol use (Reboussin et al., 2012), surveillance of occupational illnesses with workplace clustering (Preisser, Arcury, and Quandt, 2003) and clusterrandomized trials with longitudinal data (Yi and Cook, 2002; Yi, Cook, and Chen, 2010). Heagerty and Zeger (1996) defined estimating equations for the associations of correlated ordinal data in an extension of Carey et al.'s method. They compared the efficiency for estimating association parameters with ALR and different marginal methods for categorical data, including second order estimating equations (Liang et al., 1992).

Orthogonalized residuals resolve certain deficiencies in ALR based on conditional residuals. In particular, although the ALR estimate of association parameter α is invariant to the order of observations within cluster, the robust estimate of $\text{var}(\hat{\alpha})$ is not (Kuk, 2004). Qaqish, Zink, and Preisser (2012) defined estimating equations for association parameters in binary data which yield parameter estimates equal to the ALR $\hat{\alpha}$ in a special case, while resolving the disadvantages of estimating α with ALR. Orthogonalized residuals are also defined to allow for a non-zero correlation between conditional residuals, which may increase the efficiency of $\hat{\alpha}$ with respect to the ALR estimate. Their method specifies estimating equations for within-cluster association parameters with outcome crossproducts conditional on both outcomes, in contrast to Carey et al. (1993)'s method, which specifies estimating equations using, for each outcome pair in a cluster, one conditional on the other.

This article presents an extension of the orthogonalized residuals method of Qaqish et al. (2012) to ordinal outcomes using the proportional odds model along with global odds ratios to model within-cluster pairwise associations. Although pairwise associations can be specified with a saturated model with global odds ratios that vary according to the cutpoints of observation pairs, this often requires a large number of parameters. With fewer parameters, and assuming that observations are similarly correlated across categories, associations among ordinal data can be specified with common global odds ratios that are independent of cutpoints (Lumley, 1996).

The proposed methodology is defined in Sections 2 and 3. An analysis using data from the orthognathic surgery study of post-operative altered sensation is described in Section 4. In particular, a marginal model is specified for simultaneous modeling of the cumulative odds of more versus less altered sensation for each outcome and the marginal associations among pairs of outcomes using global odds ratios. A simulation study to compare the efficiency of

the proposed method to that of Heagerty and Zeger (1996) is described in Section 5. Discussion and conclusions are provided in Section 6.

2. Alternating Logistic Regressions for Ordinal Data

2.1. Model

Let O_{ij} be the ordinal response for observation j in cluster i , for $i = 1, \dots, K$, where cluster i has n_i observations. This response has $C + 1$ levels or possible realizations, so that $O_{ij} = c$ for some $c \in 1, \dots, C + 1$. The O_{ij} represent clustered responses, for example, longitudinal responses over time or multiple patient responses. Now let $\mathbf{Y}_{ij}$ be a vector representation of O_{ij} with binary elements $Y_{ij}^{(c)} = I(O_{ij} \leq c)$ $c = 1, \dots, C$, so that $\mathbf{Y}_{ij} = (Y_{ij}^{(1)}, \dots, Y_{ij}^{(C)})'$. Ordinal data are often modeled assuming proportional odds (McCullagh, 1980). For covariate vector $\mathbf{X}_{ij}$, the proportional odds model assumes that the effect of $\mathbf{X}_{ij}$ is the same across levels of O_{ij} :

$$\text{logit} \{E(Y_{ij}^{(c)} | \mathbf{X}_{ij})\} = \delta_c + \mathbf{X}_{ij}' \bar{\beta}, \quad 1 \leq c \leq C, \quad 1 \leq j \leq n_i. \quad (1)$$

The proportional odds assumption is easily relaxed by assuming a more general form for $E(Y_{ij}^{(c)} | \mathbf{X}_{ij})$ whereby the response/covariate relationship of $\bar{\beta}$ (or its components) is allowed to depend on response level c (Stokes, Davis, and Koch, 2012). A marginal model for O_{ij} with structure (1) is assumed in this article, with additional interest in pairwise global

odds $\psi_{ijk}^{(a,b)} = \frac{P(Y_{ij}^{(a)}=1, Y_{ik}^{(b)}=1) P(Y_{ij}^{(a)}=0, Y_{ik}^{(b)}=0)}{P(Y_{ij}^{(a)}=1, Y_{ik}^{(b)}=0) P(Y_{ij}^{(a)}=0, Y_{ik}^{(b)}=1)}$ where $1 \leq a, b \leq C, 1 \leq j < k \leq n_i$ (Heagerty and Zeger, 1996). A generalized linear model (with link function and linear predictor) for $\psi_{ijk}^{(a,b)}$ is governed by a q -dimensional parameter α for covariate vector $\mathbf{Z}_{ijk}^{(a,b)}$, where

$$\log(\psi_{ijk}^{(a,b)}) = \mathbf{Z}_{ijk}^{(a,b)'} \alpha, \quad 1 \leq j < k \leq n_i, \quad 1 \leq a, b \leq C. \quad (2)$$

Global odds ratios $\psi_{ijk}^{(a,b)} = \psi_{ijk}$, independent of cutpoints a and b , are often assumed, which allow for parsimonious modeling of association structures, which can otherwise involve many parameters for ordinal data (Dale, 1986; Williamson, Kim, and Lipsitz, 1995; Lumley, 1996; Williamson and Kim, 1996; Kuk, 2007). The marginal model for data O_{ij} is jointly specified by (1) and (2).

2.2. Estimation

Let $\mu_{ij} = E(Y_{ij} | \mathbf{X}_{ij})$ $\mu_i = (\mu'_{i1}, \dots, \mu'_{in_i})'$, $\delta = (\delta_1, \dots, \delta_C)'$ and $\beta = (\delta', \bar{\beta}')$. For the observed vector $\mathbf{Y}_i = (Y'_{i1}, \dots, Y'_{in_i})'$, generalized estimating equations (Liang and Zeger, 1986) estimates the mean parameter β with the solution to

$$\mathbf{U}_\beta = \sum_{i=1}^k \mathbf{D}_i' \mathbf{V}_i^{-1} (\mathbf{Y}_i - \mu_i) = 0, \quad (3)$$

where $\mathbf{D}_i = \mu_i' / \beta$ and μ_i is determined by (1). In addition to matrix $\mathbf{V}_i \approx \text{var}(\mathbf{Y}_i)$. In alternating logistic regressions (ALR) for binary data, $\mathbf{V}_i$ is parameterized in terms of odds ratios for response pairs (Carey et al., 1993).

The odds ratio $\psi_{ijk}^{(a,b)}$ determines the conditional expected value $\zeta_{ijk}^{(a,b)} = E(Y_{ij}^{(a)} | Y_{ik}^{(b)})$ (Mardia, 1967). While estimating β through (3), ALR uses another set of estimating equations based on the conditional residuals $Y_{ij}^{(a)} - \zeta_{ijk}^{(a,b)}$ to estimate association parameter α . Let ζ_{ijk} and ζ_i be vectors of conditional expectations of dimensions C^2 and $C^2 n_i(n_i - 1)/2$, respectively, such that $\zeta_{ijk} = (\zeta_{ijk}^{(1,1)}, \dots, \zeta_{ijk}^{(1,C)}, \dots, \zeta_{ijk}^{(2,1)}, \dots, \zeta_{ijk}^{(C,C)})'$ and $\zeta_i = (\zeta'_{i12}, \dots, \zeta'_{i1n_i}, \zeta'_{i23}, \dots, \zeta'_{i(n_i-1)n_i})'$. Also let vector $\mathbf{Y}_i^*$ represent observations associated with ζ_i , so that $\mathbf{Y}_{ij}^* = (\mathbf{Y}_{ij} \otimes \mathbf{1}_C)$ and $\mathbf{Y}_i^* = (\mathbf{Y}_{i1}^{*'}, \dots, \mathbf{Y}_{i1}^{*'}, \dots, \mathbf{Y}_{i2}^{*'}, \dots, \mathbf{Y}_{i(n_i-1)}^{*'})'$. As defined by Heagerty and Zeger (1996) in ALR for multi-level data, α is estimated by the solution to

$$\mathbf{U}_{\alpha, ALR} = \sum_{i=1}^K \partial \zeta_i' / \partial \alpha \text{ Dialog} \{ \zeta_i (1 - \zeta_i) \} (\mathbf{Y}_i^* - \zeta_i) = 0. \quad (4)$$

As for the generalized estimating equations of Liang and Zeger (1986), only the mean and covariance structures are explicitly specified for O_{ij} , and estimates of β and α are obtained by iteration, in this case, between (3) and (4). The resulting estimates $\hat{\alpha}$ and $\hat{\beta}$ are consistent for α and β such that for $\theta = (\beta', \alpha')'$, $\sqrt{K}(\hat{\theta} - \theta)$ is asymptotically multivariate normal with mean zero, given that (2) and (1) hold. If (2) does not hold, the outcome covariance is misspecified, and $\hat{\beta}$ is still consistent for β . Sandwich estimators based on (3) and (4) are available for the variances of $\hat{\beta}$ and $\hat{\alpha}$ (Heagerty and Zeger, 1996). A reformulation of Carey et al.'s (1993) ALR for binary data was defined by Qaqish et al. (2012) resolving the dependence of variance estimates on observation order. In the next section, a generalization of the orthogonalized residuals method developed by Qaqish et al. (2012) is introduced for ordinal data.

3. Orthogonalized Residuals

Similar to Heagerty and Zeger's ALR, our proposed reformulation based on orthogonalized residuals (ORTH) is an extension of Liang and Zeger's (1986) method, estimating marginal mean parameter β with the solution to (3). Unlike ALR, where estimation of association parameter α is based on conditional expectations $E(Y_{ij}^{(a)} | Y_{ik}^{(b)})$, α estimation is instead based on expectations of cross-products $Y_{ij}^{(a)} Y_{ik}^{(b)}$ conditional on $Y_{ij}^{(a)}$ and $Y_{ik}^{(b)}$ for $1 \leq a, b$

C and $1 \leq j < k < n_i$. Define $\mu_{ijk}^{(a,b)} = E(Y_{ij}^{(a)} Y_{ik}^{(b)})$ and $\mu_{ij}^{(a)} = E(Y_{ij}^{(a)})$. Let $T_{ijk}^{(a,b)}$ be a residual based on the conditional expectation $E(Y_{ij}^{(a)} Y_{ik}^{(b)} | Y_{ij}^{(a)}, Y_{ik}^{(b)})$ under a linearity property (Qaqish et al., 2012), such that

$$\begin{aligned} T_{ijk}^{(a,b)} &= Y_{ij}^{(a)} Y_{ik}^{(b)} - \left\{ \mu_{ijk}^{(a,b)} + b_{ijk:k}^{(a,b)} (Y_{ij}^{(a)} - \mu_{ij}^{(a)}) + b_{ijk:k}^{(a,b)} (Y_{ik}^{(b)} - \mu_{ik}^{(b)}) \right\} \text{ for} \\ d_{ijk}^{(a,b)} &= \sigma_{ijj}^{(a)} \sigma_{ikk}^{(b)} - \sigma_{ijk}^{(a,b)2}, b_{ijk:k}^{(a,b)} \\ &= \mu_{ijk}^{(a,b)} (1 - \mu_{ik}^{(b)}) (\mu_{ik}^{(b)} - \mu_{ijk}^{(a,b)}) \\ &= \mu_{ijk}^{(a,b)} (1 - \mu_{ij}^{(a)}) (\mu_{ij}^{(a)} - \mu_{ijk}^{(a,b)}) \\ &= \text{var}(Y_{ij}^{(a)}) = \mu_{ij}^{(a)} (1 - \mu_{ij}^{(a)}) \quad \text{and} \quad \sigma_{ijk}^{(a,b)}: \\ &= \text{cov}(Y_{ij}^{(a)}, Y_{ik}^{(b)}) = \mu_{ijk}^{(a,b)} \\ &\quad - \sigma_{ij}^{(a)} \mu_{ik}^{(b)} \end{aligned}$$

the $C^2 n_i (n_i - 1)/2 \times 1$ vector T_i have

elements $T_{ijk}^{(a,b)}$ such that $T_i = \left(t_{i12}^{(1,1)}, \dots, T_{i12}^{(1,C)}, T_{i12}^{(2,1)}, \dots, T_{i(n_i-1)n_i}^{(C,C)} \right)'$ For matrices

$S_i = E(-\partial T_i / \partial \alpha')$ and $P_i \approx \text{var}(T_i)$, the ORTH estimate of α is the solution to

$$U_{\alpha, ORTH} = \sum_{i=1}^K S_i' P_i^{-1} T_i = 0. \quad (5)$$

The variance of T_i is approximated by P_i , having elements cov

$$\begin{aligned} (T_{ijk}^{(a,b)}, T_{ij'k'}^{(c,d)}) &= 0 \quad \text{for } j \neq j' \quad \text{or } k \neq k', \text{ so that } P_i \text{ is block diagonal with cov} \\ (T_{ijk}^{(a,b)}, T_{ij'k'}^{(c,d)}), &\text{ whose derivation is available in web appendix A.} \end{aligned}$$

For this approximation of $\text{var}(T_i)$, ORTH estimates of β and α are obtained by iterating between (3) and (5). The resulting $\hat{\alpha}$ and $\hat{\beta}$ are consistent for $\theta = (\beta, \alpha)'$, such that

$\sqrt{K}(\hat{\theta} - \theta)$ is asymptotically multivariate normal with mean zero, given that the model defined by (2) and (1) holds. A heuristic argument for the asymptotic distribution of $\sqrt{K}(\hat{\theta} - \theta)$ is given in web appendix B.

Both orthogonalized residuals and alternating logistic regressions have inefficient estimates of α relative to second order estimating equations (Liang et al., 1992; Qaqish et al., 2012), which estimate β and α parameters simultaneously (in each iterative step). There is a considerable computational advantage to estimating α and β iteratively, where matrices of order n^2 are inverted, instead of inverting matrices of order n^4 as in second order estimating equations, for clusters of size n (Carey et al., 1993).

Although it is expected that ORTH and ALR would be less efficient than second order estimating equations, it is also expected that ORTH could gain efficiency in $\hat{\alpha}$ compared to ALR owing to its non-diagonal structure for the covariance of $\mathbf{T}_i$ in (5), and also because the residual $\mathbf{T}_i$ has a small correlation with $\mathbf{Y}_i$ (Qin and Lawless, 1994; Qaqish et al., 2012). In addition, the method proposed here has several advantages relative to the method proposed by Heagerty and Zeger (1996). First, unlike the Heagerty and Zeger (1996) estimate, the resulting $\text{var}(\hat{\alpha})$ based on (5) is invariant to the ordering of elements within cluster. The ORTH $\sqrt{K}(\hat{\theta} - \theta)$ is also estimated with a non-stochastic derivative matrix, allowing the application of standard estimating equation theory to improve efficiency even further by introducing a non-independence working correlation structure into $\mathbf{P}_i$ (not pursued here) following Qaqish et al. (2012).

4. Example

The methods described above are illustrated in an analysis of clinical trial data from a study of sensory retraining to address sensation loss following jaw surgery. This study was designed to compare perceived altered sensation for post-operative patients in two treatment groups. Both groups received standard treatment following a bilateral sagittal split osteotomy, a surgical procedure on the mandible, while one group also received an additional treatment of sensory retraining exercises (Phillips et al., 2007).

The following model represents three categorical outcomes observed over three time points, where $j = 1, \dots, 9$ indexes observation and t_j indexes time corresponding to observation j , with response $O_{ij} = c$ for some $c \in 1, \dots, C + 1$. For the example of sensory retraining data, O_{ij} is an ordinal measurement of altered sensation with seven levels ($C = 6$) where $O_{ij} = 1$ indicated the most favorable outcome and $O_{ij} = 7$ the least favorable. As in an earlier analyses of these data (Preisser et al., 2011), the seven levels were collapsed into three levels ($C = 2$) for the analysis reported here. Therefore, the pair of binary elements

$Y_{ij}^{(1)} = I(O_{ij} \leq 1)$ and $Y_{ij}^{(2)} = I(O_{ij} \leq 2)$ represent O_{ij} .

Perceived altered sensation was measured with O_{ij} over time, where O_{ij} measured the loss of lip sensitivity for $j = 1, 4, 7$, the level of unusual feelings for $j = 2, 5, 8$, and numbness for $j = 3, 6, 9$. Each of these three responses was recorded before surgery and at three subsequent times. The pre-surgical responses are not used in this analysis because there is very little variation among them. Time or visit is indexed by t_j , at planned equal times across patients, for six ($t_j = 1; j = 1, 2, 3$), 13 ($t_j = 2; j = 4, 5, 6$), and 26 ($t_j = 3; j = 7, 8, 9$) weeks after surgery. There were 93 patients in the standard treatment group and 91 patients in the sensory retraining group. Overall 178 (97%) patients had observed outcomes at all visits.

In the analysis of the sensory retraining data, the marginal mean of binary indicators $Y^{(c)}$ are initially specified by

$$\begin{aligned}
& \text{logit} \left\{ E \left(Y_{ij}^{(c)} | \mathbf{X}_{ij} \right) \right\} \\
& = \delta_c + \beta_{0U} U_{ij} + \beta_{0N} N_{ij} + \beta_{12} I(t_j=2) + \beta_{13} I(t_j=3) \\
& + \beta_{21} T_i I(t_j=1) + \beta_{22} T_i I(t_j=2) + \beta_{23} T_i I(t_j=3) \\
& + \beta_{1U2} I(U_{ij}=1, t_j=2) + \beta_{1N2} I(N_{ij}=1, t_j=2) \\
& + \beta_{1U3} I(U_{ij}=1, t_j=3) + \beta_{1N3} I(N_{ij}=1, t_j=3) \quad (6) \\
& + \beta_{2U1} I(U_{ij}=1, t_j=1) T_i + \beta_{2U2} I(U_{ij}=1, t_j=2) T_i \\
& + \beta_{2U3} I(U_{ij}=1, t_j=3) T_i + \beta_{2N1} I(N_{ij}=1, t_j=1) T_i \\
& + \beta_{2N2} I(N_{ij}=1, t_j=2) T_i + \beta_{2N3} I(N_{ij}=1, t_j=3) T_i \\
& + \beta_3 G_i + \beta_4 J_i,
\end{aligned}$$

for integers $1 = c = 2$ and $1 = j = 9$. Covariate $U_{ij} = 1$ if observation j represents the ordinal response for unusual feelings and 0 otherwise, and $N_{ij} = 1$ when j indicates a response for numbness and 0 otherwise; lip sensitivity is the reference outcome. Covariate $T_i = 1$ if subject i was in the sensory retraining group, and 0 otherwise, $G_i = 1$ if subject i received genioplasty as part of surgery (0 otherwise), and $J_i = 1$ if the surgery for subject i involved only one jaw (0 if both jaws operated on) (Phillips et al., 2007). The model parameters for the linear predictors of each time, treatment, and outcome combination are shown in Table 1. This model is saturated in time and treatment for each outcome. Thus, this model allows that the marginal mean of each outcome varies by treatment group over time. This model also allows the odds of altered sensation to differ initially by genioplasty or number of jaws in surgery, however, the corresponding rates of change in the odds of altered sensation over time are not allowed to vary in this model.

In addition to (6), the model for $Y_{ij}^{(c)}$ includes a restriction on the pairwise odds ratio between $Y_{ij}^{(a)}$ and $Y_{ij}^{(b)}$, where ij, ik indices j, k represent observations at t_j and t_k , respectively, and $1 = a, b = C$. Assuming common global odds ratios, a pre-liminary model for $\psi_{ijk}^{(a,b)} = \psi_{ijk}$ saturated by observation pair (j, k) has nine parameters: three parameters that allow for the association between $Y_{ij}^{(a)}$ and $Y_{ij}^{(b)}$ to vary by response pair (j, k) within time (α_{012} , α_{013} , and α_{023} in equation (7)), one parameter for each outcome when it is measured at different time points, and one parameter for each pair of outcomes measured at different times. A Wald test based on ORTH with value 2.50 ($p = 0.645$) indicated that associations between response measurements observed at different times can be expressed with two log odds ratios, one representing the same outcome observed at different times (α_1), and the other representing different altered sensation outcomes observed at different times (α_2), reducing the modeled association to

$$\begin{aligned}
\log(\psi_{ijk}) & = \alpha_{012} I(L_j=1, U_k=1; t_k=t_j) \\
& + \alpha_{013} I(L_j=1, N_k=1; t_k=t_j) \\
& + \alpha_{023} I(U_j=1, N_k=1; t_k=t_j) \quad (7) \\
& + \alpha_1 I(j=k; t_k \neq t_j) + \alpha_2 I(j \neq k; t_k \neq t_j),
\end{aligned}$$

for $j = k$ and $L_j = 1$ indicates that observation j relates to lip sensitivity, except the case that $j = k$. The Wald test that $\alpha_{012} = \alpha_{013} = \alpha_{023}$ has test statistic 14.30 ($p < 0.001$) with two degrees of freedom, indicating that further model reduction on this basis is not appropriate.

In equation (6), to test whether the effect of time and treatment vary for different outcomes, a Wald test that $\beta_{1U_t} = \beta_{1N_t} = 0$ for $t = 2, 3$ and that $\beta_{2U_t} = \beta_{2N_t} = 0$ for $t = 1, 2, 3$ can be used. This test has observed statistic 7.87 with ten degrees of freedom and $p = 0.642$, so the marginal mean model can be reduced to

$$\begin{aligned} \text{logit} \left\{ E \left(Y_{ij}^{(c)} | \mathbf{X}_{ij} \right) \right\} \\ = \delta_c + \beta_{0U} U_{ij} + \beta_{0N} N_{ij} + \beta_{12} I(t_j=2) \\ + \beta_{13} I(t_j=3) + \beta_{21} I(t_j=1) T_i + \beta_{22} I(t_j=2) T_i \\ + \beta_{23} I(t_j=3) T_i + \beta_3 G_i + \beta_4 J_i, \end{aligned} \quad (8)$$

for $c = 1, 2$ and $1 \leq j \leq 9$. The resulting parameter estimates for this model using both ALR as defined by Heagerty and Zeger (1996) and the proposed orthogonalized residuals for ordinal data are in Table 2.

Note that positive parameter estimates from (8) in Table 2 are associated with smaller, or more favorable, values of O_{ij} . Note also that although the change over time of different altered sensation outcomes did not vary (as restricted by (8)), the outcomes themselves varied, with patients most likely to have favorable (small) values for unusual feelings (β_{0U}), and least likely to have favorable values for numbness (β_{0N}).

The effect of the sensory retraining exercises on altered sensation relative to standard treatment is represented by β_{21} , β_{22} , and β_{23} . Although none of these parameter estimates are significantly different from zero by themselves (at 0.05), a Wald test based on ORTH that $\beta_{21} = \beta_{22} = \beta_{23} = 0$ has an observed statistic of 10.67 with three degrees of freedom and $p = 0.014$. This result suggests that the course of altered sensation over time for the two treatment groups may vary, although interpretations are not straight forward given the parameter estimates.

The parameter estimates for the global odds ratio model are also in Table 2. Given the log scale, the ORTH estimates represent odds ratios between outcome pairs from 6.5 ($\exp\{\hat{\alpha}_{012}\}$) to 15.2 ($\exp\{\hat{\alpha}_{023}\}$). The parameter α_{012} is the log odds of a more favorable result for lip sensitivity given that unusual feelings are reduced within a visit, while α_{023} is the log odds of having reduced unusual feelings given that numbness is reduced within visit. Likewise, α_{013} is the log odds of more favorable lip sensitivity given that numbness is reduced within visit, and α_1 is the log odds that one altered sensation measurement will be lower given that another is lower for the same outcome at a different visit. The parameter α_2 is the log odds that one altered sensation measurement will be lower given that another is lower for a different outcome at a different visit. The orthogonalized residuals estimate of $\boldsymbol{\alpha} = (\alpha_{012}, \alpha_{013}, \alpha_{023}, \alpha_1, \alpha_2)'$ corresponds to the estimated odds ratios (95% confidence intervals): 6.52 (4.37,9.72), 12.27 (7.70,19.56), 15.69 (9.88,24.92), 6.13 (4.51,8.33), and 3.87 (2.90,5.15). These estimates indicate that altered sensation outcomes are strongly related within time, and generally to a lesser extent, across time.

Also of interest in this analysis is whether the precision of association parameter estimates in the orthogonalized residual formulation is improved relative to ALR as proposed by Heagerty and Zeger (1996). The ratios of estimated variances for parameter estimates in

Table 2 are 101, 85, 87, 93 and 91% for $\hat{\alpha}_{012}$, $\hat{\alpha}_{013}$, $\hat{\alpha}_{023}$, $\hat{\alpha}_1$ and $\hat{\alpha}_2$, respectively, where a ratio of less than 100% indicates that the variance estimated with the orthogonalized residuals is smaller than that for ALR.

5. Simulation

5.1. Simulation Design

The relative efficiency of ALR to ORTH in finite samples and balanced cluster sizes $n_i = n$ for all i is investigated with simulated data modeled similarly to the example data from the sensory retraining study. Categorical response data O_{ij} is generated with three ($C = 2$) levels and either three or nine responses per subject $i = 1, \dots, K$, with the marginal mean of $Y_{ij}^{(c)} = I(O_{ij} = c)$ dependent on j and dichotomous covariate T_i , indicating treatment group. For $n = 9$ responses, we simulate data similar to the sensory retraining study, for three distinct outcomes observed at three times, that are similarly affected by treatment, such that the conditional expectation of $Y_{ij}^{(c)}$ is restricted by (8) and (7) for $\delta = (-0.5, 2.4)'$, $\bar{\beta} = (0.3, -0.9, 0.7, 1.2, -0.2, .3, .5, 0.0)'$ and $\alpha = (2.2, 2.9, 3.0, 0, 0)'$. In the scenarios with $n = 3$ responses, the distribution of $Y_{ij}^{(c)}$ is determined by

$$\text{logit} \left\{ E \left(Y_{ij}^{(c)} | T_i \right) \right\} = \delta_c + \beta_{0j} + \beta_{2j} T_i, \quad (9)$$

$$\log \{ \psi_{ijk} \} = \alpha_{012} I(j=1, k=2) + \alpha_{013} I(j=1, k=3) + \alpha_{023} I(j=2, k=3), \quad (10)$$

for $1 \leq j < k \leq 3$, and $c = 1, 2$, where $\beta_{01} = 0$. Values for $\delta = (\delta_1, \delta_2)'$, $\bar{\beta} = (\beta_{02}, \beta_{03}, \beta_{21}, \beta_{22}, \beta_{23})'$, and $\alpha = (\alpha_{012}, \alpha_{013}, \alpha_{23})'$ are taken from an analysis of the sensory retraining data at the last visit, yielding $\delta = (-0.5, 2.4)'$, $\bar{\beta} = (0.5, -0.6, 0.6, 0.2, 0.4)'$ and $\alpha = (2.2, 2.9, 3.0)'$.

For scenarios where $n = 3$ and $n = 9$, correlated ordinal data are generated by specifying the first two moments of $(O_{i1}, O_{i2}, O_{i3})'$ defined above using the method defined by Gange (1995) given these δ , $\bar{\beta}$, and α , for $K = 50, 100$ or 200 subjects. In all scenarios, half of subjects will have $T_i = 1$, and the remaining half will have $T_i = 0$. The correct models are used to analyze each of one thousand realizations, and a and the standard errors of α will be estimated with both ALR for ordinal data as defined by Heagerty and Zeger (1996) and orthogonalized residuals.

In order to evaluate the relative performance of orthogonalized residuals and ALR, they will be compared in the estimated bias of $\hat{\alpha}$ and the Monte Carlo standard errors of $\hat{\alpha}$. The relative efficiency of $\hat{\alpha}$ from the two methods in particular is of interest, and will be approximated here by the ratio of Monte Carlo variances of $\hat{\alpha}$, where the Monte Carlo

variance of a_{0JK} for $\sum_{s=1}^{1000} \left(\hat{\alpha}_{0jk}^{(s)} - \bar{\alpha}_{0jk} \right)^2 / 999$. In addition to these results for $\bar{\alpha}_{0jk} = \sum_{s=1}^{1000} \hat{\alpha}_{0jk}^{(s)} / 1000$, results relating to the estimated standard errors of $\hat{\alpha}$ will also be included. The bias of the standard error estimates relative to the Monte Carlo standard errors

of $\hat{\alpha}$ will be estimated, together with the coverage of nominally 95% confidence intervals for $\hat{\alpha}$, estimated by the percent of 95% confidence intervals that include the true value of α .

5.2. Simulation Results

The bias and Monte Carlo standard error of $\hat{\alpha}$ is in Table 3. Note that the bias of $\hat{\alpha}$ is reduced with increasing K (as expected), and that the bias of ORTH is always less than the bias of ALR for $n = 3$, and generally less for $n = 9$, although the percent relative bias of $\hat{\alpha}$ never exceeds 4% for either method. The Monte Carlo standard error for $\hat{\alpha}$ in ORTH is also always less than that for ALR for more than 50 clusters. The estimated efficiency of ALR relative to ORTH ranges from 92% to 100%.

The bias of standard error estimators and the coverage of nominally 95% confidence intervals are shown in Table 3. Although the difference in coverage rates of ORTH and ALR confidence intervals is not large, it is notable that the coverage for ORTH is as close or closer to the nominal coverage rate than for ALR in eight of nine cases for small clusters, and in six of nine cases for larger clusters. Also note that the bias of standard error estimators is always less than zero, so that the standard error of $\hat{\alpha}$ was underestimated by both ORTH and ALR. The absolute bias of the ORTH standard error estimator, however, is essentially the same or smaller than the absolute bias of the ALR estimator for $n = 9$, and always smaller for $n = 3$.

6. Discussion

This article considered a recently introduced methodology shown to perform well for binary data and proposed an extension of that methodology to correlated ordinal data. The proposed method was illustrated with a clinical trial for patient recovery from jaw surgery, where facial sensation was observed in three distinct ordinal outcomes over time. In simulations, the proposed method consistently outperformed alternating logistic regressions for ordinal data as defined by Heagerty and Zeger (1996).

Although efficiency was improved relative to ALR for ordinal data, the improvement of the proposed method for larger clusters was less than that for small clusters. In addition, we expect efficiency relative to ALR as defined by Heagerty and Zeger (1996) would be increased for data with more ordinal levels ($C > 2$). In practice, convergence for such data can be a feasibility issue for both ALR and ORTH, an issue which arose in the course of this study when analyzing simulated data (not shown). The more complex structure of the covariance matrix of ORTH appears to affect computation time, because these matrices need to be inverted, and for ALR their diagonal structure makes inversion less burdensome computationally. This difference in computing time was observed for the sensory retraining example at 6 seconds for ALR, and forty seconds for ORTH.

Our study is also limited by the scenarios chosen for simulated data, which do not include missing observations within clusters. Like alternating logistic regressions and common implementations of generalized estimating equations, the proposed method requires missing observations (such as person-visits in a longitudinal study) to be completely missing at random or covariate-dependent. Extensions of ORTH to missing at random (MAR) dropout

may be possible along the lines of Yi et al. (2010) using inverse probability weights under a model for MAR dropout.

Simulation results show an advantage of ORTH over ALR in a subset of finite samples. In addition, the proposed method's analytic properties allow for representation of the estimating equations for α in a standard form (i.e., equation (5)) and permit the use of non-diagonal working covariance matrix $\mathbf{P}_i$ to provide a more efficient estimator of α . We conjecture that further efficiency gains are possible by introducing non-zero off-diagonal block elements of $\mathbf{P}_i$, for example, through a working correlation structure as proposed by Qaqish et al. (2012) for binary data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Model parameters for the linear predictors in the marginal mean model for each time, treatment, and outcome combination in the Sensory Retraining example

Outcome	Time	Tx	Model linear predictor*
lip	1	0	δ_c
	2	0	$\delta_c + 0 + \beta_{12}$
	3	0	$\delta_c + 0 + \beta_{13}$
	1	1	$\delta_c + 0 + 0 + \beta_{21}$
	2	1	$\delta_c + 0 + \beta_{12} + \beta_{22}$
	3	1	$\delta_c + 0 + \beta_{13} + \beta_{23}$
unusual	1	0	$\delta_c + \beta_{0U}$
	2	0	$\delta_c + \beta_{0U} + \beta_{12} + 0 + \beta_{1U2}$
	3	0	$\delta_c + \beta_{0U} + \beta_{13} + 0 + \beta_{1U3}$
	1	1	$\delta_c + \beta_{0U} + 0 + \beta_{21} + 0 + \beta_{2U1}$
	2	1	$\delta_c + \beta_{0U} + \beta_{12} + \beta_{22} + \beta_{1U2} + \beta_{2U2}$
	3	1	$\delta_c + \beta_{0U} + \beta_{13} + \beta_{23} + \beta_{1U3} + \beta_{2U3}$
numbness	1	0	$\delta_c + \beta_{0N}$
	2	0	$\delta_c + \beta_{0N} + \beta_{12} + 0 + \beta_{1N2}$
	3	0	$\delta_c + \beta_{0N} + \beta_{13} + 0 + \beta_{1N3}$
	1	1	$\delta_c + \beta_{0N} + 0 + \beta_{21} + 0 + \beta_{2N1}$
	2	1	$\delta_c + \beta_{0N} + \beta_{12} + \beta_{22} + \beta_{1N2} + \beta_{2N2}$
	3	1	$\delta_c + \beta_{0N} + \beta_{13} + \beta_{23} + \beta_{1N3} + \beta_{2N3}$

* Linear predictor for the marginal mean model in equation (6) of a subject who did not receive genioplasty ($G_i = 0$) as part of surgery involving both jaws ($J_i = 0$). The bold parameters were included in the initial model but not in the final model.

Table 2

Estimates and estimated standard errors for marginal mean and pairwise log odds ratio parameters with ALR and orthogonalized residuals in the Sensory Retraining example. ALR estimates were calculated by the Heagerty and Zeger (1996) formulation, and the ORTH estimates are those proposed above.

Variable		ALR		ORTH	
		Est	SE	Est	SE
Intercept 1	δ_1	-1.956	0.2394	-1.951	0.2392
Intercept 2	δ_2	0.633	0.2294	0.635	0.2293
Unusual feelings (ref: lip sensitivity)	β_{0U}	0.234	0.0999	0.233	0.1000
Numbness (ref: lip sensitivity)	β_{0N}	-0.795	0.0947	-0.795	0.0947
13 weeks (ref: 6 weeks)	β_{12}	0.667	0.1299	0.661	0.1296
26 weeks (ref: 6 weeks)	β_{13}	1.392	0.1749	1.387	0.1748
Common trt effect (6 weeks)	β_{21}	-0.302	0.2394	-0.303	0.2394
Common trt effect (13 weeks)	β_{22}	0.369	0.2425	0.370	0.2426
Common trt effect (26 weeks)	β_{23}	0.362	0.2388	0.362	0.2389
Genioplasty	β_3	0.324	0.2099	0.324	0.2100
One jaw (ref: two jaws)	β_4	0.433	0.2025	0.434	0.2025
Lip sensitivity and unusual feelings	α_{012}	1.927	0.2035	1.874	0.2043
Lip sensitivity and numbness	α_{013}	2.399	0.2580	2.508	0.2378
Unusual feelings and numbness	α_{023}	2.762	0.2523	2.753	0.2359
Same outcome, different times	α_1	1.740	0.1623	1.814	0.1565
Different outcomes, different times	α_2	1.376	0.1532	1.353	0.1464

Table 3

Relative bias, Monte Carlo standard errors, estimated relative efficiency, coverage of nominal 95% confidence intervals, and average bias of estimated standard error for ALR and ORTH estimates of association parameter $\alpha = (\alpha_{012}, \alpha_{013}, \alpha_{023})' = (2, 2, 2, 9, 3)'$ for simulated ordinal data. For data with $\mathbf{K} = 50, 100$ or 200 clusters, with three and nine responses, having marginal mean (9) and association (10).

	K	Bias of $\hat{\alpha}$			Monte Carlo SE			ALR Est. efficiency			Coverage of 95% CI			Bias of $\hat{\alpha}$		
		ALR	ORTH		ALR	ORTH		ALR	ORTH		ALR	ORTH		ALR	ORTH	
		Cluster size 3														
$\hat{\alpha}_{012}$	50	0.045	0.034	0.758	0.759	1.00	85.3	88.6		-0.128	-0.121					
	100	0.038	0.027	0.519	0.508	95.8	91.1	92.2		-0.077	-0.065					
	200	0.019	0.015	0.353	0.347	96.6	92.9	92.9		-0.038	-0.035					
$\hat{\alpha}_{013}$	50	0.072	0.061	0.794	0.776	97.7	75.6	75.7		-0.054	-0.031					
	100	0.077	0.067	0.581	0.564	94.2	93.7	94.1		-0.056	-0.042					
	200	0.037	0.031	0.389	0.374	92.4	94.6	94.8		-0.024	-0.015					
$\hat{\alpha}_{023}$	50	0.028	0.013	0.802	0.776	96.7	95.4	95.1		0.020	0.050					
	100	0.108	0.098	0.633	0.623	96.9	95.2	95.5		-0.035	-0.029					
	200	0.063	0.054	0.480	0.465	93.8	92.6	93.3		-0.067	-0.057					
Cluster size 9																
$\hat{\alpha}_{012}$	50	-0.020	-0.029	0.387	0.383	98.9	89.8	90.0		-0.050	-0.049					
	100	-0.004	-0.010	0.275	0.273	99.2	91.6	90.7		-0.037	-0.038					
	200	-0.003	-0.004	0.185	0.182	98.6	92.5	92.7		-0.016	-0.017					
$\hat{\alpha}_{013}$	50	0.054	0.053	0.513	0.497	96.7	95.8	95.6		-0.029	-0.018					
	100	0.028	0.029	0.347	0.337	97.4	94.9	95.8		-0.010	-0.007					
	200	0.002	0.004	0.248	0.242	97.1	93.5	93.9		-0.013	-0.012					
$\hat{\alpha}_{023}$	50	0.036	0.031	0.517	0.510	98.7	92.8	93.6		-0.066	-0.065					
	100	0.020	0.018	0.332	0.322	97.1	93.6	94.8		-0.018	-0.014					
	200	0.005	0.001	0.237	0.229	96.4	93.5	93.3		-0.017	-0.014					