R Package multgee: A Generalized Estimating Equations Solver for Multinomial Responses

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Abstract

This vignette of the R package multgee is an updated version of Touloumis (2015), published in the Journal of Statistical Software. To cite multgee in publications, please use Touloumis (2015). To cite the GEE methodology implemented in multgee, please use Touloumis, Agresti, and Kateri (2013).

The R package multgee implements the local odds ratios generalized estimating equations (GEE) approach proposed by Touloumis et al. (2013), a GEE approach for correlated multinomial responses that circumvents theoretical and practical limitations of the GEE method. A main strength of multgee is that it provides GEE routines for both ordinal (ordLORgee) and nominal (nomLORgee) responses, while relevant software in R and SAS are restricted to ordinal responses under a marginal cumulative link model specification. In addition, multgee offers a marginal adjacent categories logit model for ordinal responses and a marginal baseline category logit model for nominal. Further, utility functions are available to ease the local odds ratios structure selection (intrinsic.pars), to construct confidence intervals (confint), to extract the variance-covariance matrix of the regression parameters (vcov) and to perform a Wald-type goodness-of-fit test between two nested GEE models (waldts). We demonstrate the application of multgee through a clinical trial with clustered ordinal multinomial responses.

Keywords: generalized estimating equations, nominal and ordinal multinomial responses, local odds ratios, R.

1. Introduction

In several studies, the interest lies in drawing inference about the regression parameters of a marginal model for correlated, repeated or clustered multinomial variables with ordinal or nominal response categories while the association structure between the dependent responses is of secondary importance. The lack of a convenient multivariate distribution for multinomial
responses and the sensitivity of ordinary maximum likelihood methods to misspecification of the association structure led researchers to modify the GEE method of Liang and Zeger (1986) in order to account for multinomial responses (Miller, Davis, and Landis 1993; Lipsitz, Kim, and Zhao 1994; Williamson, Kim, and Lipsitz 1995; Lumley 1996; Heagerty and Zeger 1996; Parsons, Edmondson, and Gilmour 2006). These GEE approaches estimate the marginal regression parameter vector by solving the same set of estimating equations as in Liang and Zeger (1986), but differ in the way they parametrize and/or estimate \( \alpha \), a parameter vector that is usually defined to describe a “working” assumption about the association structure.

Touloumsis et al. (2013) showed that the joint existence of the estimated marginal regression parameter vector and \( \hat{\alpha} \) cannot be assured in existing approaches. This is because the parametric space of the proposed parameterizations of the association structure depends on the marginal model specification even in the simple case of bivariate multinomial responses. To address this issue, Touloumsis et al. (2013) defined \( \alpha \) as a “nuisance” parameter vector that contains the marginalized local odds ratios structure, that is the local odds ratios as if no covariates were recorded, and they employed the family of association models (Goodman 1985) to develop parsimonious and meaningful structures regardless of the response scale. The practical advantage of the local odds ratios GEE approach is that it is applicable to both ordinal and nominal multinomial responses without being restricted by the marginal model specification. Simulations in Touloumsis et al. (2013) imply that the local odds ratios GEE approach captures a significant portion of the underlying correlation structure, and compared to the independence “working” model (i.e., assuming no correlation structure in the GEE methodology), simple local odds ratios structures can substantially increase the efficiency gains in estimating the regression vector of the marginal model. Note that low convergence rates for the GEE approach of Lipsitz et al. (1994) and Heagerty and Zeger (1996) did not allow the authors to compare these approaches with the local odds ratios GEE approach while the GEE approach of Parsons et al. (2006) was excluded from the simulation design because its use is restricted to a cumulative logit marginal model specification.

The R (R Core Team 2019) package multgee implements the local odds ratios GEE approach and it is available from the Comprehensive R Archive Network at https://CRAN.R-project.org/package=multgee. To emphasize the importance of reflecting the nature of the response scale on the marginal model specification and on the marginalized local odds ratios structure, two core functions are available in multgee: nomLORgee which is appropriate for GEE analysis of nominal multinomial responses and ordLORgee which is appropriate for ordinal multinomial responses. In particular, options for the marginal model specification include a baseline category logit model for nominal response categories and a cumulative link model or an adjacent categories logit model for ordinal response categories. In addition, there are six utility functions that enable the user to: i) Perform goodness-of-fit tests between two nested GEE models (waldts), ii) construct Wald type confidence intervals (confint), iii) select the local odds ratios structure based on the rule of thumb discussed in Touloumsis et al. (2013) (intrinsic.pars), iv) obtain the estimated covariance matrix of the parameter estimates (vcov), v) construct a probability table (to be passed in the core functions) that satisfies a desired local odds ratios structure (matrixLOR), and vi) obtain commonly used criteria for variables and/or association structure selection in the GEE literature.

To appreciate the features of multgee, we briefly review GEE software for multinomial responses in SAS (SAS Institute Inc. 2014) and R. The current version of SAS supports only the independence “working” model under a marginal cumulative probit or logit model for ordinal
multinomial responses. To the best of our knowledge, SAS macros (Williamson, Lipsitz, and Kim 1998; Yu and Yuan 2004) implementing the approach of Williamson et al. (1995) are not publicly available. The R package repolr (Parsons 2013) implements the approach of Williamson et al. (2006) but it is restricted to using a cumulative logit model. Another option for ordinal responses is the function ordgee in the R package geepack (Halekoh, Højsgaard, and Yan 2006). This function implements the GEE approach of Heagerty and Zeger (1996) but it seems to produce unreliable results for multinomial responses. To illustrate this, we simulated independent multinomial responses under a cumulative probit model specification with a single time-stationary covariate for each subject and we employed ordgee to obtain the GEE estimates from the independence “working” model. Description of the generative process can be found in Scenario 1 of Toulomis et al. (2013) except that we used the values −3, −1, 1 and 3 for the four category specific intercepts in order to make the problem more evident. Based on 1000 simulation runs when the sample size $N = 500$, we found that the bias of the GEE estimate of $\beta = 1$ was $\approx 4.8 \times 10^{28}$, indicating the presence of a bug or -at least- of numerical problems for some situations. Similar problems occurred for the alternative global odds ratios structures in ordgee. In contrast to existing software, multgee offers greater variety of GEE models for ordinal responses, implements a GEE model for nominal responses and is not limited to the independence “working” model, which might lead to significant efficiency losses. Further, one can assess the goodness of fit for two or more nested GEE models.

This paper is organized as follows. In Section 2, we present the theoretical background of the local odds ratios GEE approach that is necessary for the use of multgee. We introduce the marginal models implemented in multgee, the estimation procedure for the “nuisance” parameter vector $\alpha$ and the asymptotic theory on which GEE inference is based. We describe the arguments of the core GEE functions (nomLORgee, ordLORgee) in Section 3 while the utility functions (waldts, confint, intrinsic.pars, vcov, matrixLOR, gee_criteria) are described in Section 4. In Section 5, we illustrate the use of multgee in a longitudinal study with correlated ordinal multinomial responses. We summarize the features of the package and provide a few practical guidelines in Section 6.

2. Local odds ratios GEE approach

For notational ease, suppose the data arise from a longitudinal study with no missing observations. However, note that the local odds ratios GEE approach is not limited neither to longitudinal studies nor to balanced designs, under the strong assumption that missing observations are missing completely at random (Rubin 1976).

Let $Y_{it}$ be the multinomial response for subject $i$ ($i = 1, \ldots, N$) at time $t$ ($t = 1, \ldots, T$) that takes values in $\{1, 2, \ldots, J\}$, $J > 2$. Define the response vector for subject $i$

$$
Y_i = (Y_{i1}, \ldots, Y_{i(J-1)}, Y_{i1(J-1)}, \ldots, Y_{i2(J-1)}, \ldots, Y_{iT1}, \ldots, Y_{iT(J-1)})^\top,
$$

where $Y_{itj} = 1$ if the response for subject $i$ at time $t$ falls at category $j$ and $Y_{itj} = 0$ otherwise. Denote by $x_{it}$ the covariates vector associated with $Y_{it}$, and let $x_i = (x_{i1}^\top, \ldots, x_{iT}^\top)^\top$ be the covariates matrix for subject $i$. Define $\pi_{itj} = E(Y_{itj}|x_i) = P(Y_{itj} = 1|x_i) = P(Y_{itj} = j|x_i)$ as the probability of the response category $j$ for subject $i$ time $t$, and let $\pi_i = (\pi_{i1}, \ldots, \pi_{it(J-1)})^\top$ be the mean vector of $Y_i$, where $\pi_{it} = (\pi_{it1}, \ldots, \pi_{it(J-1)})^\top$. It follows from the above that $Y_{itJ} = 1 - \sum_{j=1}^{J-1} Y_{itj}$ and $\pi_{itJ} = 1 - \sum_{j=1}^{J-1} \pi_{itj}$.
2.1. Marginal models for correlated multinomial responses

The choice of the marginal model depends on the nature of the response scale. For ordinal multinomial responses, the family of cumulative link models

\[ F^{-1}[P(Y_{it} \leq j|x_i)] = \beta_{j0} + \beta_j^T x_{it} \]  

(1)

or the adjacent categories logit model

\[ \log \left( \frac{\pi_{itj}}{\pi_{it(j+1)}} \right) = \beta_{j0} + \beta_j^T x_{it} \]  

(2)

can be used, where \( F \) is the cumulative distribution function of a continuous distribution and \( \{\beta_{j0} : j = 1, \ldots, J - 1\} \) are the category specific intercepts. For nominal multinomial responses, the baseline category logit model

\[ \log \left( \frac{\pi_{itj}}{\pi_{itJ}} \right) = \beta_{j0} + \beta_j^T x_{it} \]  

(3)

can be used, where \( \beta_j \) is the \( j \)-th category specific parameter vector.

It is worth mentioning that the linear predictor differs in the above marginal models. First, the category specific intercepts need to satisfy a monotonicity condition \( \beta_{10} \leq \beta_{20} \leq \cdots \leq \beta_{(J-1)0} \) only when the family of cumulative link models in (1) is employed. Second, the regression parameter coefficients of the covariates \( x_{it} \) are category specific only in the marginal baseline category logit model (3) and not in the ordinal marginal models (1) and (2).

2.2. Estimation of the marginal regression parameter vector

To unify the notation, let \( \beta \) be the \( p \)-variate parameter vector that includes all the regression parameters in (1), (2) or (3). To obtain \( \hat{\beta}_G \), a GEE estimator of \( \beta \), Touloumis et al. (2013) solved the estimating equations

\[ U(\beta, \hat{\alpha}) = \frac{1}{N} \sum_{i=1}^N D_i V_i^{-1}(Y_i - \pi_i) = 0 \]  

(4)

where \( D_i = \partial \pi_i / \partial \beta \) and \( V_i \) is a \((J-1) \times (J-1) \) “weight” matrix that depends on \( \beta \) and on \( \hat{\alpha} \), an estimate of the “nuisance” parameter vector \( \alpha \) defined formally in Section 2.3. Succinctly, \( V_i \) is a block matrix that mimics the form of \( \text{COV}(Y_i|x_i) \), the true covariance matrix for subject \( i \). The \( t \)-th diagonal matrix of \( V_i \) is the covariance matrix of \( Y_{it} \) determined by the marginal model. The \((t, t')\)-th off-diagonal block matrix describes the marginal pseudo-association of \( (Y_{it}, Y_{it'}) \), which is a function of the marginal model and of the pseudo-probabilities \( \{P(Y_{it} = j, Y_{it'} = j'|x_i) : j, j' = 1, \ldots, J - 1\} \) calculated based on \((\hat{\alpha}, \beta)\). We should emphasize that \( V_i \) is a “weight” matrix because \( \alpha \) is defined as a “nuisance” parameter vector and it is unlikely to describe a valid “working” assumption about the association structure for all subjects.

2.3. Estimation of the nuisance parameter vector and of the weight matrix

Order the \( L = T(T-1)/2 \) time-pairs with the rightmost element of the pair most rapidly varying as \((1,2),(1,3), \ldots, (T-1,T)\), and let \( G \) be the group variable with levels the \( L \)
ordered pairs. For each time-pair \((t, t')\), ignore the covariates and cross-classify the responses across subjects to form an \(J \times J\) contingency table such that the row totals correspond to the observed totals at time \(t\) and the column totals to the observed totals at time \(t'\), and let \(\theta_{ijt'j'}\) be the local odds ratio at the cutpoint \((j,j')\) based on the expected frequencies \(\{f_{ijt'j'}: j, j' = 1, \ldots, J\}\). For notational reasons, let \(A\) and \(B\) be the row and column variable respectively. Assuming a Poisson sampling scheme to the \(L\) sets of \(J \times J\) contingency tables, fit the RC-G(1) type model \((\text{Becker and Clogg 1989})\)

\[
\log f_{ijt'j'} = \lambda + \lambda_j^A + \lambda_j^B + \lambda_{(t,t')}^G + \lambda_{j(t,t')}^G + \lambda_{j'(t,t')}^G + \phi^{(t,t')} \mu_j^{(t,t')} \mu_j^{(t,t')} \beta_{ijt'j'},
\]

(5)

where \(\{\mu_j^{(t,t')} : j = 1, \ldots, J\}\) are the score parameters for the \(J\) response categories at the time-pair \((t,t')\). After imposing identifiability constraints on the regression parameters in (5), the log local odds ratios structure is given by

\[
\log \theta_{ijt'j'} = \phi^{(t,t')} \left( \mu_j^{(t,t')} - \mu_j^{(t,t') + 1} \right) \left( \mu_j^{(t,t')} - \mu_j^{(t,t') + 1} \right).
\]

(6)

At each time-pair, (6) summarizes the local odds ratios structure in terms of the \(J\) score parameters and the intrinsic parameter \(\phi^{(t,t')}\) that measures the average association of the marginalized contingency table. Since the score parameters do not need to be fixed or monotonic, the local odds ratios structure is applicable to both nominal and ordinal multinomial responses.

\textbf{Touloumis et al. (2013)} defined \(\alpha\) as the parameter vector that contains the marginalized local odds ratios structure

\[
\alpha = \left( \theta_{1121}, \ldots, \theta_{1(J-1)2(J-1)}, \ldots, \theta_{(T-1)1(T-1)}, \ldots, \theta_{(T-1)(J-1)(T)(J-1)} \right)^T
\]

where \(\theta_{ijt'j'}\) satisfy (6). To increase the parsimony of the local odds ratios structures for ordinal responses, they proposed to use common unit-spaced score parameters \(\mu_j^{(t,t')} = j\) and/or common intrinsic parameters \(\phi^{(t,t')} = \phi\) across time-pairs. For a nominal response scale, they proposed to apply a homogeneity constraint on the score parameters \(\mu_j^{(t,t')} = \mu_j\) and use common intrinsic parameters across time-pairs. To estimate \(\alpha\) maximum likelihood methods are involved by treating the \(L\) marginalized contingency tables as independent. Technical details and justification about this estimation procedure can be found in \textbf{Touloumis (2011)} and \textbf{Touloumis et al. (2013)}.

Conditional on the estimated marginalized local odds ratios structure \(\hat{\alpha}\) and the marginal model specification at times \(t\) and \(t'\), \(\{P(Y_{it} = j, Y_{it'} = j'|x_i) : t < t', j, j' = 1, \ldots, J - 1\}\) are obtained as the unique solution of the iterative proportional fitting (IPF) procedure \((\text{Deming and Stephan 1940})\). Hence, \(V_i\) can be readily calculated and the estimating equations in (4) can be solved with respect to \(\beta\).

\subsection*{2.4. Asymptotic properties of the GEE estimator}

Given \(\hat{\alpha}\), inference about \(\beta\) is based on the fact that \(\sqrt{N}(\hat{\beta}_G - \beta) \sim N(0, \Sigma)\) asymptotically, where

\[
\Sigma = \lim_{N \to \infty} N \Sigma_0^{-1} \Sigma_1 \Sigma_0^{-1},
\]

(7)
\[ \Sigma_0 = \sum_{i=1}^{N} D_i^\top V_i^{-1} D_i \quad \text{and} \quad \Sigma_1 = \sum_{i=1}^{N} D_i^\top V_i^{-1} \text{COV}(Y_i|X_i) V_i^{-1} D_i. \]

For finite sample sizes, \( \hat{\Sigma} \) is estimated by ignoring the limit in (7) and replacing \( \beta \) with \( \hat{\beta}_G \) and \( \text{COV}(Y_i|X_i) \) with \( (Y_i - \hat{\pi}_i)(Y_i - \hat{\pi}_i)^\top \) in \( \Sigma_0 \) and \( \Sigma_1 \). In the literature, \( \hat{\Sigma}/N \) is often termed as “sandwich” or “robust” covariance matrix of \( \hat{\beta}_G \).

3. Description of core functions

We describe the arguments of the functions nomLORgee and ordLORgee, focusing on the marginal model specification (formula, link), data representation (id, repeated, data) and local odds ratios structure specification (LORstr, LORterm, homogeneous, restricted). For completeness’ sake, we also present computational related arguments (LORem, add, bstart, LORgee_control, ipfp.control, IM). The two core functions share the same arguments, except link and restricted which are available only in ordLORgee, and they both create an object of the class LORgee which admits summary, coef, update, vcov, confint and residuals methods.

3.1. Marginal model specification

For ordinal multinomial responses, the link argument in the function ordLORgee specifies which of the marginal models (1) or (2) will be fitted. The options “logit”, “probit”, “cauchit” or “cloglog” indicate the corresponding cumulative distribution function \( F \) in the cumulative link model (1), while the option “acl” implies that the adjacent categories logit model (2) is selected. For nominal multinomial responses, the function nomLORgee fits the baseline category logit model (3), and hence the link argument is not offered.

The formula (= response ~ covariates) argument identifies the multinomial response variable (response) and specifies the form of the linear predictor (covariates), assuming that this includes an intercept term. If required, the \( J > 2 \) observed response categories are sorted in an ascending order and then mapped onto \( \pi_1, \ldots, \pi_J \). To account for a covariate \( x \) with a constrained parameter coefficient fixed to 1 in the linear predictor, the term offset(\( x \)) must be inserted on the right hand side of formula.

3.2. Data representation

The id argument identifies the \( N \) subjects by assigning a unique label to each subject. If required, the observed id labels are sorted in an ascending order and then relabeled as \( 1, \ldots, N \), respectively.

The repeated argument identifies the times at which the multinomial responses are recorded by treating the \( T \) unique observed times in the same manner as in id. The purpose of repeated is dual: To identify the \( T \) distinct time points and to construct the full marginalized contingency table for each time-pair by aggregating the relevant/available responses across subjects. The repeated argument is optional and it can be safely ignored in balanced designs or in unbalanced designs in which if the \( t \)-th response is missing for a particular subject then all subsequent responses at times \( t' > t \) are missing for that subject. Otherwise, it is recommended to provide the repeated argument in order to ensure proper construction of the full marginalized contingency table. To this end, note that if the measurement occasions are not recorded in a numerical mode, then the user should create repeated by mapping the
Table 1: The main options for the marginalized local odds ratios structures in `multgee`.

| log $\theta_{tj't'}$ | LORstr          | Functions | Parameters |
|----------------------|-----------------|-----------|------------|
| $\phi$               | "uniform"      | ordLORgee | 1          |
| $\phi^{(t,t')}$      | "category.exch"| ordLORgee | L          |
| $\phi^{(t,t')}(\mu_j - \mu_{j+1}) (\mu_{j'} - \mu_{j'+1})$ | "time.exch" | Both      | $J-1$      |
| $\phi^{(t,t')}(\mu_j^{(t,t')} - \mu_{j+1}^{(t,t')}) (\mu_{j'}^{(t,t')} - \mu_{j'+1}^{(t,t')})$ | "RC"            | Both      | $L(J-1)$ |

3.3. Marginalized local odds ratios structure specification

The marginalized local odds ratios is specified via the LORstr argument. Table 1 displays the structures proposed by Touloumis et al. (2013). Currently the default option is the time exchangeability structure ("time.exch") in nomLORgee and the category exchangeability ("category.exch") structure in ordLORgee. The uniform ("uniform") and category exchangeability structures are not allowed in nomLORgee because given unit-spaced parameter scores are not meaningful for nominal response categories.

The user can also fit the independence “working” model (LORstr = "independence") or even provide the local odds ratios structure (LORstr = "fixed") using the LORterm argument. In this case, an $L \times J^2$ matrix must be constructed such that the $g$-th row contains the vectorized form of a probability table that satisfies the desired local odds ratios structure at the time-pair corresponding to the $g$-th level of $G$.

Touloumis (2011) discussed two further versions of the "time.exch" and the RC ("RC") structures based on using: i) Heterogeneous score parameters (homogeneous = FALSE) at each time-pair, and/or ii) monotone score parameters (restricted = TRUE), an option applicable only for ordinal response categories. However, it is sensible to employ these additional options only when the local odds ratios structures in Table 1 do not seem adequate.

It is important to mention that the user must provide only the arguments required for the specified local odds ratios structure. For example, the arguments homogeneous, restricted and LORterm are ignored when LORstr = "uniform".

3.4. Computational details

The default estimation procedure for the marginalized local odds ratios structure is to fit model (5) to the full marginalized contingency table (LORem = "3way") after imposing the
desired restrictions on the intrinsic and the score parameters. Touloumis (2011) noticed that the estimated local odds ratios structure under model (5) is identical to that obtained by fitting independently a row and columns (RC) effect model (Goodman 1985) with homogeneous score parameters to each of the $L$ contingency tables. Motivated by this, an alternative estimation procedure (LORem = "2way") for estimating the structures "uniform" and "time.exch" was proposed. In particular, one can estimate the single parameter of the "uniform" structure as the average of the $L$ intrinsic parameters $\phi(t,t')$ obtained by fitting the linear-by-linear association model (Agresti 2013) independently to each of the $L$ marginalized contingency tables. For the "time.exch" structure, one can fit $L$ RC effects models with homogeneous (homogeneous = TRUE)/heterogeneous (homogeneous = FALSE) score parameters and then estimate the log local odds ratio at each cutpoint $(j, j')$ by averaging $\log \hat{\theta}_{j,j'}$ for $t < t'$. Regardless of the value of LORem, the appropriate model for counts is fitted via the function gnm of the R package gnm (Turner and Firth 2012).

In the presence of zero observed counts, a small positive constant can be added (add) at each cell of the marginalized contingency table to ensure the existence of $\tilde{\alpha}$. We conjecture that a constant of the magnitude $10^{-4}$ will serve this purpose without affecting the strength of the association structure.

A Fisher scoring algorithm is employed to solve the estimating equations (4) as in Lipsitz et al. (1994). The only difference is that now $\tilde{\alpha}$ is not updated. The default way to obtain the initial value for $\beta$ is via the function vglm of the R package VGAM (Yee 2010). Alternatively, the initial value can be provided by the user (bstart). The Fisher scoring algorithm converges when the elementwise maximum relative change in two consecutive estimates of $\beta$ is less than or equal to a predefined positive constant $\epsilon$. The control argument controls the related iterative procedure variables and printing options. The default maximum number of iterations is 15 and the default tolerance is $\epsilon = 0.001$.

Recall that calculation of the “weight” matrix $V_i$ at given values of $(\beta, \alpha)$ relies on the IPF procedure. The ipfp.ctrl argument controls the related variables. The convergence criterion is the maximum of the absolute difference between the fitted and the target row and column marginals. By default, the tolerance of the IPF procedure is $10^{-6}$ with a maximal number of iterations equal to 200.

The IM argument defines which of the R functions solve, qr.solve or cholesky will be used to invert matrices in the Fisher scoring algorithm.

4. Description of utility functions

The function waldts performs a goodness-of-fit test for two nested GEE models based on a Wald test statistic. Let $M_0$ and $M_1$ be two nested GEE models with marginal regression parameter vectors $\beta_0$ and $\beta_1 = (\beta_0^T, \beta_q^T)^T$, respectively. Define a matrix $C$ such that $C\beta_1 = \beta_q$. Here $q$ equals the rank of $C$ and the dimension of $\beta_q$. The hypothesis

$$H_0 : \beta_q = 0 \text{ vs } H_1 : \beta_q \neq 0$$

tests the goodness-of-fit of $M_0$ versus $M_1$. Based on a Wald type approach, $H_0$ is rejected at $\alpha\%$ significance level, if $(C\hat{\beta})^T(NC\hat{\Sigma}C^T)^{-1}(C\hat{\beta}) \geq X_q(\alpha)$, where $\hat{\beta}$ and $\hat{\Sigma}$ are estimated under model $M_1$ and $X_q(\alpha)$ denotes the $\alpha$ upper quantile of a chi-square distribution with $q$ degrees of freedom.
The function confint calculates the Wald-type confidence intervals for the regression parameters of the marginal model under consideration. The method argument specifies whether the standard errors of the regression parameters estimates will be derived from the “sandwich” (method = "robust") or the “model-based” (method = "naive") covariance matrix. The default is to use the “sandwich” covariance matrix.

Touloumis et al. (2013) suggested to select the local odds ratios structure by inspecting the range of the $L$ estimated intrinsic parameters under the "category.exch" structure for ordinal responses, or under the "RC" structure for nominal responses. If the estimated intrinsic parameters do not differ much, then the underlying marginalized local odds ratios structure is likely nearly exchangeable across time-pairs. In this case, the simple structures "uniform" or "time.exch" should be preferred because they tend to be as efficient as the more complicated ones. The function intrinsic.pars gives the estimated intrinsic parameter of each time-pair.

The function vcov returns the “sandwich” (method = "robust") or the “model-based” (method = "naive") covariance matrix. The default is to use the “sandwich” covariance matrix. It is used internally to calculate confidence intervals for the regression parameters and to compare nested models.

The single-argument function matrixLOR creates a two-way probability table that satisfies a desired local odds ratios structure. This function aims to ease the construction of the LORterm argument in the core functions nomLORgee and ordLORgee.

For completeness, the function gee_criteria reports commonly used criteria for variable selection and for selecting the “working” association structure. The Quasi Information Criterion (QIC) proposed by Pan (2001), the Correlation Information Criterion (CIC) proposed by Hin and Wang (2009) and the Rotnitzky and Jewell’s Criterion (RJC) proposed by Rotnitzky and Jewell (1990) are used for selecting the best association structure. The QICu criterion (Pan 2001) is used for selecting the best subset of covariates. When choosing among GEE models with different association structures but with the same subset of covariates, the model with the smallest value of QIC, CIC or RJC should be preferred. However, note that these criteria might not be very useful for multinomial GEE models with local odds ratios structures and the user should prefer the empirical rule suggested in Touloumis et al. (2013) and implemented in intrinsic.pars. When choosing between two or more GEE models with different number of covariates that are not nested, the model with the smallest QICu value should be preferred. The function gee_criteria can be used to obtain the values for the above criteria for one or more models of the class LORgee.

5. Example

To illustrate the main features of the package multgee, we follow the GEE analysis performed in Touloumis et al. (2013). The data came from a randomized clinical trial (Lipsitz et al. 1994) that aimed to evaluate the effectiveness of the drug Auranofin versus the placebo therapy for the treatment of rheumatoid arthritis. The five-level (1=poor, . . . , 5=very good) ordinal multinomial response variable was the self-assessment of rheumatoid arthritis recorded at one ($t = 1$), three ($t = 2$) and five ($t = 3$) follow-up months. To acknowledge the ordinal response
The marginal cumulative logit model
\[
\log \left( \frac{P(Y_{it} \leq j | x_i)}{1 - P(Y_{it} \leq j | x_i)} \right) = \beta_{j0} + \beta_1 I(time_i = 3) + \beta_2 I(time_i = 5) + \beta_3 trt_i + \beta_4 I(b_i = 2) + \beta_5 I(b_i = 3) + \beta_6 I(b_i = 4) + \beta_7 I(b_i = 5). \quad (8)
\]
was fitted, where \( i = 1, \ldots, 301, \ t = 1, 2, 3, \ j = 1, 2, 3, 4 \) and \( I(A) \) is the indicator function for the event \( A \). Here \( x_i \) denotes the covariates matrix for subject \( i \) that includes the self-assessment of rheumatoid arthritis at the baseline \( (b_i) \), the treatment variable \( (trt_i) \), coded as (1) for the placebo group and (2) for the drug group, and the follow-up time recorded in months \( (time_i) \).

The GEE analysis is performed in two steps. First, we select the marginalized local odds ratios structure by estimating the intrinsic parameters under the "category.exch" structure

```r
R> library("multgee")

Loading required package: gnm

R> data("arthritis")
R> head(arthritis)
          id y sex age trt baseline time
1        1 4 2   54 2   2   1
2        2 1 5   54 2   2   3
3        3 1 5   54 2   2   5
4        4 2 4  1  41 1   3   1
5        5 2 4  1  41 1   3   3
6        6 2 4  1  41 1   3   5

R> intrinsic.pars(y = y, data = arthritis, id = id, repeated = time, +
  rscale = "ordinal")

[1] 0.6517843 0.9097341 0.9022272
```

The range of the estimated intrinsic parameters is small (≈ 0.26) which suggests that the underlying marginalized association pattern is nearly constant across time-pairs. Thus we expect the "uniform" structure to capture adequately the underlying correlation pattern. Note that we passed the time variable to the repeated argument because this numerical variable indicates the measurement occasion at which each observation was recorded.

Now we fit the cumulative logit model (8) under the "uniform" via the function `ordLORgee`

```r
R> fit <- ordLORgee(formula = y ~ factor(time) + factor(trt) + factor(baseline), +
  link = "logit", id = id, repeated = time, data = arthritis, +
  LORstr = "uniform")
R> summary(fit)
```
GEE FOR ORDINAL MULTINOMIAL RESPONSES
version 1.6.0 modified 2017-07-10

Link: Cumulative logit

Local Odds Ratios:
Structure: uniform
Model: 3way
call:
ordLORgee(formula = y ~ factor(time) + factor(trt) + factor(baseline),
   data = arthritis, id = id, repeated = time, link = "logit",
   LORstr = "uniform")

Summary of residuals:

|          | Min. | 1st Qu. | Median | Mean  | 3rd Qu. | Max.               |
|----------|------|---------|--------|-------|---------|-------------------|
|          | -0.5161111 | -0.2399227 | -0.0749670 | 0.0000219 | -0.0066995 | 0.9932912        |

Number of Iterations: 5

Coefficients:

|        | Estimate | san.se | san.z  | Pr(>|san.z|) |
|--------|----------|--------|--------|-------------|
| beta10 | -1.84315 | 0.38929 | -4.7346 | < 2e-16 *** |
| beta20 | 0.26692  | 0.35013 | 0.7624  | 0.44585     |
| beta30 | 2.23132  | 0.36625 | 6.0924  | < 2e-16 *** |
| beta40 | 4.52542  | 0.42123 | 10.7434 | < 2e-16 *** |
| factor(time)3 | 0.00140 | 0.12183 | 0.0115  | 0.99080     |
| factor(time)5 | -0.36172 | 0.11395 | -3.1743 | 0.00150 **  |
| factor(trt)2 | -0.51212 | 0.16799 | -3.0486 | 0.00230 **  |
| factor(baseline)2 | -0.66963 | 0.38036 | -1.7605 | 0.07832 .   |
| factor(baseline)3 | -1.26070 | 0.35252 | -3.5763 | 0.00035 *** |
| factor(baseline)4 | -2.64373 | 0.41282 | -6.4041 | < 2e-16 *** |
| factor(baseline)5 | -3.96613 | 0.53164 | -7.4602 | < 2e-16 *** |
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Local Odds Ratios Estimates:

```
[,1] [,2] [,3] [,4] [,5] [,6] [,7] [,8] [,9] [,10] [,11] [,12]
[1,]  0.000  0.000  0.000  0.000  2.257  2.257  2.257  2.257  2.257  2.257  2.257  2.257
[2,]  0.000  0.000  0.000  0.000  2.257  2.257  2.257  2.257  2.257  2.257  2.257  2.257
[3,]  0.000  0.000  0.000  0.000  2.257  2.257  2.257  2.257  2.257  2.257  2.257  2.257
[4,]  0.000  0.000  0.000  0.000  2.257  2.257  2.257  2.257  2.257  2.257  2.257  2.257
[5,]  2.257  2.257  2.257  2.257  0.000  0.000  0.000  0.000  2.257  2.257  2.257  2.257
[6,]  2.257  2.257  2.257  2.257  0.000  0.000  0.000  0.000  2.257  2.257  2.257  2.257
[7,]  2.257  2.257  2.257  2.257  0.000  0.000  0.000  0.000  2.257  2.257  2.257  2.257
[8,]  2.257  2.257  2.257  2.257  0.000  0.000  0.000  0.000  2.257  2.257  2.257  2.257
[9,]  2.257  2.257  2.257  2.257  2.257  2.257  2.257  2.257  0.000  0.000  0.000  0.000
```
The summary method summarizes the fit of the GEE model including the GEE estimates, their estimated standard errors based on the “sandwich” covariance matrix and the p-values from testing the statistical significance of each regression parameter in (8). The estimated marginalized local odds ratios structure can be found in a symmetric $T(J - 1) \times T(J - 1)$ block matrix written symbolically as

$$
\begin{bmatrix}
0 & \Theta_{12} & \ldots & \Theta_{1T} \\
\Theta_{21} & 0 & \ldots & \Theta_{2T} \\
\vdots & \vdots & \ddots & \vdots \\
\Theta_{T1} & \Theta_{T2} & \ldots & 0
\end{bmatrix}
$$

Each block denotes an $(J - 1) \times (J - 1)$ matrix. The $(j, j')$-th element of the off-diagonal block $\Theta_{tt'}$ represents the estimate of $\theta_{jj'}$. Based on the properties of the local odds ratios it is easy to see that $\Theta_{tt'} = \Theta_{t't}$ for $t < t'$. Finally, the diagonal blocks are zero to reflect the fact that no local odds ratios are estimated when $t = t'$. In our example, $J = 5$ and thus each block is a $4 \times 4$ matrix. Since the uniform structure is selected, all local odds ratios are equal and estimated as 2.257. Finally, the value of Null model corresponds to the $p$-value of testing the hypothesis that no covariate is significant, i.e., $\beta_1 = \beta_2 = \beta_3 = \beta_4 = \beta_5 = \beta_6 = \beta_7 = 0$, based on a Wald test statistic.

Goodness-of-fit of model (8) can be tested by comparing it to a marginal cumulative logit model that additionally contains the age and gender main effects in the linear predictor

R> fit1 <- update(fit, formula = ~ . + factor(sex) + age)
R> waldts(fit, fit1)

Goodness of Fit based on the Wald test

Model under H_0: y ~ factor(time) + factor(trt) + factor(baseline)
Model under H_1: y ~ factor(time) + factor(trt) + factor(baseline) + factor(sex) + age

Wald Statistic = 3.9554, df = 2, p-value = 0.1384

Alternatively, we can compare these two models using commonly used criteria:

R> gee_criteria(fit, fit1)

| QIC     | CIC | RJC | QICu | Parameters |
|---------|-----|-----|------|------------|
| fit     | 1264.325 | 1264.312 | 11.0066 | 1.2740 | 11 |
| fit1    | 1275.860 | 1275.703 | 13.0785 | 0.9785 | 13 |
The Wald confidence intervals for the regression parameters of the reduced model are:

\[
R > \text{confint}(\text{fit})
\]

| Parameter            | 2.5 %          | 97.5 %         |
|----------------------|---------------|----------------|
| beta10               | -2.6061497    | -1.08015721    |
| beta20               | -0.4193163    | 0.95314883     |
| beta30               | 1.5134867     | 2.94915281     |
| beta40               | 3.6998267     | 5.35101277     |
| factor(time)3        | -0.2373805    | 0.24018865     |
| factor(time)5        | -0.5850535    | -0.13837735    |
| factor(trt)2         | -0.8413778    | -0.18287050    |
| factor(baseline)2    | -1.4151270    | 0.07587068     |
| factor(baseline)3    | -1.9516257    | -0.56978096    |
| factor(baseline)4    | -3.4528305    | -1.83462340    |
| factor(baseline)5    | -5.0081187    | -2.92413445    |

6. Summary and practical guidelines

We described the R package `multgee` which implements the local odds ratios GEE approach (Touloumis et al. 2013) for correlated multinomial responses. Unlike existing GEE softwares, `multgee` allows GEE models for ordinal (`ordLORgee`) and nominal (`nomLORgee`) responses. The available local odds ratios structures (`LORstr`) in each function respect the nature of the response scale to prevent usage of ordinal local odds ratios structures (e.g., "uniform") in `nomLORgee`. The fitted GEE model is summarized via the `summary` method while the estimated regression coefficient can be retrieved via the `coef` method. The statistical significance of the regression parameters can be assessed via the function `waldts`. Confidence intervals of a desired marginal model can be obtained by the function `confint`. A similar strategy to that presented in Section 5, can be adopted to analyze GEE models for correlated nominal multinomial responses.

From a practical point of view, we recommend the use of the "uniform" structure for ordinal responses and the "time.exch" structure for nominal especially when the range of the estimated intrinsic parameters (`intrinsic.pars`) is small. Based on our experience, some convergence problems might occur as the complexity of the local odds ratios structure increases and/or if the marginalized contingency tables are very sparse. Two possible solutions are either to adopt a simpler local odds ratios structure or to increase slightly the value of the constant added to the marginalized contingency tables (`add`). However, we believe that users should refrain from using the independence “working” model unless the aforementioned strategies fail to remedy the convergence problems. To decide on the form of the linear predictor, variable selection model procedures could be incorporated using the function `waldts`. Finally, confidence intervals could be obtained by using the function `confint`.

In future versions of `multgee`, we plan to permit time-dependent intercepts in the marginal models, to increase the range of the marginal models, by including, for example, the family of continuation-ratio models for ordinal responses, and to offer a function for assessing the proportional odds assumption in models (1) and (2).
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