A Class of Markov Models for Longitudinal Ordinal Data

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SUMMARY. Generalized linear models with serial dependence are often used for short longitudinal series. Heagerty(2002) has proposed marginalized transition models for the analysis of longitudinal binary data. In this paper, we extend this work to accommodate longitudinal ordinal data. Fisher-scoring algorithms are developed for estimation. Methods are illustrated on quality of life data from a recent colorectal cancer clinical trial.

KEY WORDS: Generalized linear models; QOL; Fisher-scoring.

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1. Introduction

Quality of life (QOL) data in clinical trials is generally obtained repeatedly over time using questionnaires that can be completed by the patient without direct supervision. We will analyze QOL data from a recent colorectal cancer clinical trial (Goldberg et al, 2004). The main objective of this trial was to find a better treatment for colorectal cancer. However, given that the toxicity profiles were quite different on the 3 treatment arms, it was of interest to see if there was a negative impact of 'better' treatments on patients QOL. In this paper we compare the quality of life on the 3 treatments. We will introduce a new regression model to answer this question using a full likelihood based approach.

Generalized linear models for longitudinal data can be classified into directly specified (marginal) models and indirectly specified (conditional) models. In marginal models, the population-averaged effect of covariates on the longitudinal response is directly specified. (Liang and Zeger, 1986; Fitzmaurice and Laird, 1993). In conditional models, the effect of covariates on responses is specified conditional on random effects or previous history of responses. So the population-averaged effect of covariates is indirectly specified (Zeger and Karim, 1991; Breslow and Clayton, 1993). Here, we focus on marginal models.

Marginalized likelihood-based models describe the correlation among observations by embedding the marginal mean structure within a complete multivariate probability model with dependence, modelled via random effects or a Markov structure. We will extend previous work using a Markov structure (Azzalini, 1994; Heagerty, 2002) to ordinal categorical data. Related models for binary data can be found in Heagerty (1999) and Miglioretti and Heagerty (2004). This class of likelihood-based directly specified marginal models have several advantages over conditional models. First, the interpretation of regression coefficients is invariant with respect to specification of the dependence in the model unlike in conditional models. In addition, they can be much less susceptible to bias resulting

from random effects model mis-specification (Heagerty and Zeger, 2000; Heagerty and Kurland, 2001).

Next, we provide a brief review of models for ordinal data on which our work will build. McCullagh (1980) proposed the cumulative logit model for independent ordinal data. A general overview of models for ordinal categorical data can be found in Liu and Agresti (2005). Most of the models for correlated ordinal data fall into two classes: those modelling dependence using the global odds ratio (GOR) (Dale, 1986) and those modelling dependence via random effects. The GOR is an extension of the simple odds ratio for a 2×2 contingency table formed when adjacent rows and columns of a $K \times K$ contingency table ($K > 2$) are collapsed into a 2×2 table. Molenberghs and Lesaffre (1994) specified the joint probability of multivariate observations through the first and higher-order marginal parameters. Williamson et al. (1995) developed marginal mean regression techniques based on the global odds ratios as a measure of association and also considered latent variable models and maximum likelihood estimation for bivariate ordinal responses. Heagerty and Zeger (1996) proposed marginal regression models for clustered ordinal data by specifying marginal means and marginal pairwise global odds ratios and used estimating equations and alternating logistic regressions for inference. In terms of random effects, Gibbons and Hedeker (1997) developed random-effects ordinal regression models for the probit and logistic links. Todem et. al. (2003) and Liu and Hedeker (2006) proposed models for multiple ordinal outcomes in longitudinal settings using random effects.

All these approaches to modelling dependence have a goal of reducing the number of dependence parameters, thereby implicitly reducing the number of probabilities that need to be estimated. For example, a saturated model (with no covariates) for a five category ordinal response measured at six occasions would require the estimation of $15,625$

multinomial probabilities. Our approach to reducing this estimation problem will be to introduce a proportional odds model for the marginal means (probabilities) and a Markov transition structure for the temporal dependence. The use of a likelihood based approach will have advantages for longitudinal data that is missing at random (MAR) and in particular, ignorable. Likelihood based inference is valid under ignorability and the missing data mechanism (mdm) need not be explicitly specified. Semiparametric GEE approaches require explicit specification of the mdm for MAR. In addition, the re-weighting based approaches (based on the mdm) to handle MAR in GEEs only 'impute' missing values at the observed data points. Likelihood based approaches do not have this restriction and allow 'imputation' of values outside the range of the observed data points via parametric distributional assumptions.

The paper is arranged as follows. In section 2, we briefly review marginalized transition models for longitudinal binary data. In section 3, we consider two marginalized transition models for the longitudinal ordinal data. Methods are illustrated on the quality of life data in section 4.

2. Review of Marginalized Transition Model

In this section, we review Heagerty's marginalized model for the analysis of longitudinal binary data (Heagerty, 2002). Let $Y_i = (Y_{i1}, \cdots, Y_{in_i})$ be binary data observed on subject $i = 1, \cdots, N$ at times $t = 1, \cdots, n_i$. We assume that associated exogenous but possibly time-varying covariates, $x_{it} = (x_{it1}, \cdots, x_{itr})$, are recorded for each subject at each time. Define $\mu_{it}^M = E(Y_{it}|X_{it})$. We assume that the regression model properly specifies the full covariate conditional mean such that $E(Y_{it}|X_{it}) = E(Y_{it}|X_{i1}, \cdots, X_{in_i})$. The pth-order

marginalized transition model, MTM(p), can be expressed through the pair of regressions

$$\text{mean model:} \quad \text{logit}\{\mu_{it}^M\} = x_{it}^T\beta, \tag{1}$$

$$\text{dependence model:} \quad \text{logit}\{\mu_{it}^c\} = \triangle_{it} + \sum_{j=1}^{p} \gamma_{itj}y_{it-j}, \tag{2}$$

where $\mu_{it}^c = E(Y_{it}|Y_{it-1}, \cdots, Y_{it-p}, X_{it})$ is the conditional mean, $\gamma_{itj} = z_{it}^T\alpha_j$ are dependence parameters describing serial dependence by quantifying how strongly the immediate past predicts the present. z_{it} is a subset of x_{it}, and the subject/time specific intercept in the conditional model, $\triangle_{it}$, is determined implicitly by X_i, β and α.

The mean parameter β describes changes in the average response as a function of covariates. Using a logistic link for the transition model, (2), implies that the parameters α_j are unconstrained. For a given mean model, (1), and dependence model, (2), the intercept $\triangle_{it}$ is fully constrained and must yield the proper marginal expectation μ_{it}^M when μ_{it}^c is averaged over the distribution of the history. Therefore, a unique $\triangle_{it}$ can be identified that satisfies both the transition model and the marginal mean assumptions given any finite-valued dependence model and probability distribution for the history.

This model has several desirable features. First, the mean model is specified separately from the dependence model. As a result, the interpretation of the regression parameter β is invariant as we modify assumptions regarding the dependence in equation (2). This is not true for classical transition models, which parameterize μ_{it}^c directly as a function of covariates. Second, the marginalized transition model can be used with data where subjects have variable lengths of follow-up, permitting likelihood analysis in settings where data may be missing at random (MAR).

Given β and α, $\triangle_{it}$ for MTM(p) is computed based on the following relationship

between the marginal and conditional means,

$$\mu_{it}^M = \sum_{j_1,\cdots,j_p} \mu_{it}^c \pi_{ij_1,\cdots,j_p}^{(t)},$$

where $\pi_{ij_1,\cdots,j_p}^{(t)} = P(Y_{it-1} = j_1, \cdots, Y_{it-p} = j_p)$. Further details are given in Heagerty (2002).

3.   Marginalized transition models for longitudinal ordinal data

In this section, we propose two marginalized transition models (MTM) for longitudinal ordinal data, a simple extension of MTM (OMTM) and an improved extension of MTM (IOMTM).

Let $Y_i = (Y_{i1}, \cdots, Y_{in_i})$ be a vector of longitudinal K-category ordinal responses on subject $i = 1, \cdots, N$ at times $t = 1, \cdots, n_i (n_i \leq T)$. We assume that associated exogenous but possibly time-varying covariates, $x_{it} = (x_{it1}, \cdots, x_{itr})$, are recorded for each subject at each time and that the regression model properly specifies the full covariate conditional probability such that $P(Y_{it} = y_{it}|X_{it}) = P(Y_{it} = y_{it}|X_{i1}, \cdots, X_{iT})$.

The *simple extension of marginalized transition model of order p*, OMTM(p), is specified using the following two regressions,

$$\text{mean model:} \quad \log\frac{P(Y_{it} \leq k|x_{it})}{1 - P(Y_{it} \leq k|x_{it})} = \beta_{0k} + \mathbf{x}_{it}^T\beta, \tag{3}$$

$$\text{dependence model:} \quad \log\frac{P(Y_{it} = k|Y_{it-1}, \cdots, Y_{it-p}, x_{it})}{P(Y_{it} = K|Y_{it-1}, \cdots, Y_{it-p}, x_{it})} = \triangle_{itk} + \sum_{m=1}^{p}\sum_{l=1}^{K-1}\gamma_{itml}^{(k)}Y_{it-m,l}, \tag{4}$$

where β is the $p \times 1$ vector of regression coefficients, $\beta_{01} < \beta_{02} < \cdots < \beta_{0K-1}$, $\gamma_{itml}^{(k)} = z_{it}\alpha_{ml}^{(k)}$, z_{it} is a subset of x_{it}, $\alpha_{ml}^{(k)} = (\alpha_{ml1}^{(k)}, \cdots, \alpha_{mlq}^{(k)})^T$, $k = 1, \cdots, K - 1$, and $Y_{i,t-m,l}$ is the set of $K - 1$ indicators with $Y_{i,t-m,l} = 1$ if $Y_{i,t-m} = l$; $Y_{i,t-m,l} = 0$ otherwise for $l = 1, \cdots, K - 1$; $m = 1, \cdots, p$. Model (3) is a cumulative logit model, a common

model for ordinal data. However, the link function in the conditional probabilities (4) is a multinomial logit since we expect the $K-1$ conditional probabilities to have different coefficients $\gamma_{itml}^{(k)}$ depending on k and if cumulative logits were used as in the marginal probabilities (3), the monotonicity property of the cumulative conditional probabilities would be difficult to satisfy as it involves $\triangle_{itk}$.

The dependence model (4) based on the multinomial logit link function models the probability of moving from category k at time t to category k' at time $t+1$ under $p=1$. This is a natural and interpretable way to model the dependence for longitudinal data. An alternative approach would be to model dependence using global odds ratios (Dale, 1986; Heagerty and Zeger, 1996) as discussed in the introduction which also allows the interpretation of marginal mean parameters to be invariant with respect to specification of the dependence and allows for parsimonious specification of dependence. However, global odds ratio do not directly represent the change over time for a subject, unlike the OMTM, and that is why we choose to specify the dependence using a Markov transition structure.

Since this model is a straightforward extension of the MTM for binary data, it shares many of the same advantages including having the attractive characterization of serial dependence that a transition model provides combined with a marginal regression structure. However, it does have some drawbacks. First, there are a lot of dependence parameters. For example, if $p=1$, $K=4$, and $q=1(z_{it}=1)$, we need $2 \times p \times (K-1)^2 \times q = 18$ dependence parameters. Second, the ordering of the categories is not exploited in the conditional probabilities (4). For these two reasons, we propose a modified version in which (4) is replaced with

$$\log \frac{P(Y_{it}=k|Y_{it-1},\cdots,Y_{it-p},x_{it})}{P(Y_{it}=K|Y_{it-1},\cdots,Y_{it-p},x_{it})} = \triangle_{itk} + c(y_{it-1},\cdots,y_{it-p};\alpha^{(k)}), \qquad (5)$$

where $c(\cdot)$ is a smooth function of $y_{it-1},\cdots,y_{it-p}$ parameterized by $\alpha^{(k)}$. For our methods

here, we chose an additive structure for $c(\cdot; \alpha^{(k)})$, i.e., $c(y_{it-1}; \alpha^{(k)}) + c(y_{it-2}; \alpha^{(k)}) + \cdots + c(y_{it-p}; \alpha^{(k)})$ and quadratic polynomials for each $c(y_{it-l}; \alpha^{(k)}) : l = 1, \ldots, p$. The quadratic polynomials should be adequate to explain the smooth change of the conditional probabilities and we hypothesize that there is no dramatic change in conditional probabilities that would necessitate higher order polynomials or other smooth functions; we discuss a more general specification in the Discussion. Implicit in this specification is the 'scoring' of the response in the dependence model, which is not an issue in the (proportional odds) mean models. For example, a quadratic model could be made more reasonable for a dataset by changing the values of the responses (but not changing their order). We replace (5) by

$$\log \frac{P(Y_{it} = k | Y_{i,t-1}, \cdots, Y_{i,t-p}, x_{it})}{P(Y_{it} = K | Y_{i,t-1}, \cdots, Y_{i,t-p}, x_{it})} = \triangle_{itk} + \sum_{m=1}^{p} \gamma_{itm1}^{(k)} Y_{i,t-m} + \gamma_{itm2}^{(k)} Y_{i,t-m}^2, \quad (6)$$

where $\gamma_{itml}^{(k)} = z_{it}^T \alpha_{ml}^{(k)}$ and $\alpha = (\alpha_{11}^T, \alpha_{12}^T, \cdots, \alpha_{p1}^T, \alpha_{p2}^T)^T$. We call the model given by equations (3) and (6) a *improved extension of MTM of order p*, IOMTM(p). The IOMTM(p) has fewer dependence parameters than the OMTM. For example, OMTM has 18 dependence parameters for $K = 4$, $p = 2$ and $q = 1$, whereas an IOMTM(1) has $2 \times 2 \times (K-1) = 12$ dependence parameters. In general, for OMTM(p), the number of dependence parameters increases quadratically with K, the number of categories, whereas in IOMTM, the number increases linearly in K. IOMTM also exploits the ordering of the categorical responses in the conditional model (6).

Clearly, for models (3)-(6) to form a coherent probability model, the $\triangle_{itk}$ will be constrained. Constraints are needed for (3), (4), and (6) to be a valid probability model. Specifically, $\triangle_{itk}$ is found using the following identity

$$\begin{aligned} P(Y_{it} = k | x_{it}) &= \sum_{g_1=1}^{K} \cdots \sum_{g_p=1}^{K} P(Y_{it} = k | Y_{it-1} = g_1, \cdots, Y_{it-p} = g_p, x_{it}) \times \\ &\qquad P(Y_{it-1} = g_1, \cdots, Y_{it-p} = g_p | x_{it-1}). \end{aligned} \quad (7)$$

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In this paper, we consider only first and second order (I)OMTM's. Higher order models are possible but require more dependence parameters and larger sample sizes.

3.1 First order models: OMTM(1) and IOMTM(1)

In this subsection, we provide some details for OMTM(1) and IOMTM(1), which are often sufficient for short time series. The dependence models for marginalized 1st order transition models (OMTM(1) and IOMTM(1)) are specified using the following two regressions,

$$\text{For OMTM(1): } \log \frac{P(Y_{it}=k|Y_{it-1},x_{it})}{P(Y_{it}=K|Y_{it-1},x_{it})} = \triangle_{itk} + \sum_{l=1}^{K-1} \gamma_{it1l}^{(k)} Y_{it-1,l}, \tag{8}$$

$$\text{For IOMTM(1): } \log \frac{P(Y_{it}=k|Y_{i,t-1},x_{it})}{P(Y_{it}=K|Y_{i,t-1},x_{it})} = \triangle_{itk} + \gamma_{it11}^{(k)} Y_{i,t-1} + \gamma_{it12}^{(k)} Y_{i,t-1}^2. \tag{9}$$

Note that (9) is only valid for $t \geq 2$ since there is no history data available for the initial state ($t=1$).

For both IOMTM(1) and OMTM(1), mean and dependence parameters are orthogonal as given in the following Theorem and Corollary.

Theorem I: The marginal mean parameters, (β_0,β) are orthogonal to the dependence parameters, α in the OMTM(1).

Corollary I: The marginal mean parameters, (β_0,β), are orthogonal to the dependence parameters, α in the IOMTM(1) when $c(y;\alpha)$ is a polynomial in y.

Fitzmaurice and Laird (1993) showed consistency of marginal mean parameters regardless of the dependence structure. This was used by Heagerty (2002) in binary MTM's. The following Theorem gives the equivalent result for ordinal MTM's.

Theorem II: The maximimum likelihood estimate, $(\hat{\beta}_0,\hat{\beta})$, remains consistent for (β_0,β) even if the dependence model is incorrectly specified.

Proofs of these results can be found in the web appendix.

3.2 *Maximum likelihood for the first order models*

The maximum likelihood algorithm for these models is described next. Define the marginal cumulative probabilities, $P_{itk}^M = P(Y_{it} \leq k | x_{it})$ for $i = 1, \cdots, N$; $t = 1, \cdots, n_i$; $k = 1, \cdots, K$ and conditional probabilities, $P_{itk}^c = P(Y_{it} = k | Y_{it-1}, x_{it})$ for $i = 1, \cdots, N$; $t = 2, \cdots, n_i$; $k = 1, \cdots, K$. The OMTM(1) likelihood function consists of two components, conditional probabilities for time > 1 and marginal probabilities at time 1,

$$L(\theta; y) = \prod_{i=1}^{N} \prod_{t=2}^{n_i} \prod_{k=1}^{K} (P_{itk}^c)^{y_{itk}} \times \prod_{i=1}^{N} \prod_{k=1}^{K} \left(\pi_{ik}^{(1)} \right)^{y_{i1k}},$$

where $\pi_{ik}^{(1)} = P_{i1k}^M - P_{i1k-1}^M$. We propose a Fisher-scoring algorithm to find the MLE of the parameters of interest in the OMTM(1). For estimation of the $K-1$ intercepts β_{0k} $(k = 1, \cdots, K-1)$, r covariate coefficients β, and $(K-1)^2$ dependence parameters α, we rewrite the log likelihood as

$$
\begin{aligned}
&\log L(\theta; y) \\
&= \sum_{i=1}^{N} \sum_{t=2}^{n_i} \left\{ \sum_{k=1}^{K-1} y_{itk} \left(\triangle_{itk} + \gamma_{it11}^{(k)} y_{it-11} + \cdots + \gamma_{it1K-1}^{(k)} y_{it-1K-1} \right) + \log P_{itK}^c \right\} \\
&\quad + \sum_{i=1}^{N} \sum_{k=1}^{K-1} \left\{ R_{i1k} \phi_{i1k} - R_{i1k+1} g(\phi_{i1k}) \right\} \\
&\overset{\text{let}}{=} \log L^{(2)}(\theta; y) + \log L^{(1)}(\theta; y),
\end{aligned}
\tag{10}
$$

where $R_{i1k} = Y_{i11} + \cdots + Y_{i1k}$, $\phi_{i1k} = \log \left(\frac{P_{i1k}^M}{P_{i1k+1}^M - P_{i1k}^M} \right)$ and $g(a) = \log \{1 + \exp(a)\}$. Here we have used the notation from McCullagh (1980) for the log likelihood function for the cumulative logit model for the ordinal data, $\log L^{(1)}$.

To evaluate the likelihood, we need to evaluate both the contribution from the initial state, $L^{(1)}$, and the subsequent contribution from each transition probability, $L^{(2)}$. Let $\theta = (\beta_0, \beta, \alpha)$ be the vector of parameters. We obtain

$$\frac{\partial \log L}{\partial \theta} = \frac{\partial \log L^{(2)}}{\partial \theta} + \frac{\partial \log L^{(1)}}{\partial \theta}.$$

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The $K - 1 + r + (K - 1)q$-dimensional likelihood equations and details on the Fisher-scoring algorithm used to solve the likelihood equations can be found in Supplementary Materials.

Estimation for the IOMTM(1) is similar.

3.3 *Second order models: OMTM(2) and IOMTM(2)*

For the initial states, we assumed a marginal model for $t = 1$, as we did for the first order models, and an OMTM(1) and IOMTM(1) for $t = 2$. The marginal models for OMTM(2) and IOMTM(2) are same as (3) and the dependence models for the OMTM(2) and the IOMTM(2) are given by (4) and (6), respectively with $p = 2$. Unlike the first order OMTM and IOMTM, the orthogonality of marginal and dependence parameters no longer holds (i.e., cannot write it in canonical log linear form). Thus, consistent estimation of the marginal mean parameters requires correct modeling of the dependence (though marginalized models of this form often offer some robustness; see Heagerty and Kurland, 2001). Details on maximum likelihood estimation for the second order models can be found in Supplementary Materials.

3.4 *Missing data*

When the data are incomplete due to dropout that is associated with observed outcomes (i.e., missing at random), the orthogonality of marginal mean and dependence parameters in the (I)OMTM(1) no longer holds. Thus, the consistency of the marginal mean parameters under MAR relies on correctly specifying the dependence structure; otherwise, the score functions for the mean parameters can be biased.

3.5 *Simulation study*

We conducted several simulation studies to examine robustness to misspecification of dependence model when there is ignorable (MAR) dropout. We set $T = 8$ and $N = 500$ with an approximately equal sample size for each of the three (treatment) groups. We

considered two different marginal mean models, (3), one with an unstructured mean over time with design vector of the form, $x_{it}^T = (0, \ldots, 1, \ldots, 0, \text{group1}_i, \text{group2}_i)$, where the 1 is in the tth slot, and one with a linear trend over time, $x_{it}^T = (\text{Visit}_{it}, \text{group1}_i, \text{group2}_i)$, where groupj$_i$ is an indicator of whether the subject was in group j. The two different mean models were included to see if any bias in the presence of dropout differed between the unstructured and structured (over time) means.

For each simulation, we considered the following MAR dropout model,

$$\text{logit} P(\text{dropout} = t | \text{dropout} \geq t) = -2.5 + 0.6 Y_{it-1} + 0.3 Y_{it-2}.$$

We simulated data using (9) with $\gamma_{it1m}^{(k)} = \alpha_{m0} + \alpha_{m1} \times \text{Visit}_{it}$, $m = 1, 2$, $(\alpha_{10}, \alpha_{11}, \alpha_{20}, \alpha_{21}) = (-1.0, 0.5, -0.5, 0.1)$ and fit the model assuming $\gamma_{it1m}^{(k)} = \alpha_{m0}$.

Table 1 presents the point estimates and the percent relative bias. Percent relative biases in the coefficients were small, the largest being about 3%. The coefficients of time-varying covariates in the structured mean model appeared to be more robust to mis-specification of dependence and MAR missingness than in the unstructured mean model.

We performed several similar simulations using the same models for the marginal means, but simulating data under an IOMTM(2) and then fitting an IOMTM(1) with and without MAR dropout. In the presence of dependence mis-specification and MAR dropout, we saw considerable bias, with relative biases as large as 74% for the unstructured mean (see Supplementary Materials for the results of these simulations). Under dependence mis-specification with no dropout, the biases were quite small despite the orthogonality of the mean and dependence parameters being lost in the IOMTM(2). These simulations further emphasize the importance of correctly specifying the dependence in the presence of missing data. We also did simulations (not shown) to examine small

sample bias in the MLE's with complete data. The bias in the mean parameters was negligible. These results can be found in (Lee, 2007).

4. Example

We use the models proposed in Section 3 to analyze QOL data from the clinical trial of metastatic colorectal cancer introduced in Section 1. A total of 795 patients with colorectal cancer were randomly assigned to one of three treatments (FOLFOX, IFL(Control), IROX) between May 1999 and April 2001 (Goldberg et al 2004). We focus on one QOL measure, fatigue. Fatigue is measured on a 5 point ordinal scale (1: I am usually not tired at all; 2: I am occasionally rather tired; 3: There are frequently periods when I am quite tired; 4: I am usually very tired; 5: I feel exhausted most of the time). Because very few patients reported category 5, we collapsed category 4 and 5 into one category. For numerical reasons, we re-scaled the response as -0.9,-0.3,0.3, and 0.9. in the dependence model; the re-scaling was not needed for the marginal mean model.

To examine treatment differences in fatigue levels, we included type of treatment(ARM1=1 for FOLFOX; ARM2=1 for IROX) and visit number(TIME=$0.0, 0.1, \cdots, 0.5$) again re-scaled. The Akaike Information Criteria(AIC) (Akaike, 1974) and likelihood ratio tests were used as the model selection criterion.

We assumed the missing responses (mostly due to dropout) were missing at random (MAR) in our initial analysis. In Section 4.2, we more carefully handled the dropouts related to the reason for dropping out (including death).

The Fisher-scoring algorithm is not trivial computationally due to the need to obtain an estimate of Δ_{it} for all subjects and at all times, within each Fisher-scoring step. However, in our dataset, with 795 patients, a four category ordinal responses, and six visit times, the computational burden was not high. Each Fisher-scoring step (in which all the Δ_{it} are computed) on a Pentium with a 1.6GHz processor took about 10 and 30 seconds

for the IOMTM(1) and the IOMTM(2), respectively. In addition, using good initial values based on fitting an independent proportional odds model in standard software results in a minimal number of iterations until convergence.

4.1 *Models Fit*

We fit and compared seven models. Three were IOMTM(1)'s, three were IOMTM(2)'s, and the other was an OMTM(1) . IOMTM(1)-1 and IOMTM(2)-1 were the simplest models, with time homogeneous dependence, $\gamma_{itj}^{(k)} = \alpha_{j0}^{(k)}$. IOMTM(1)-2 and IOMTM(2)-2 allowed the dependence coefficients to depend on Time, $\gamma_{itj}^{(k)} = \alpha_{j0}^{(k)} + \alpha_{j1}^{(k)} \times \text{visit}_{it}$. IOMTM(1)-3 and IOMTM(2)-3 had dependence parameters depending on treatment, $\gamma_{itj}^{(k)} = \alpha_{j0}^{(k)} + \alpha_{j2}^{(k)} \times \text{Arm1}_i + \alpha_{j3}^{(k)} \times \text{Arm2}_i$. The OMTM was an OMTM(1) with time homogeneous dependence model, $\gamma_{itj}^{(k)} = \alpha_{j0}^{(k)}$ for $j = 1, 2, 3$.

Table 2 presents maximum likelihood estimates for all seven models. Point estimates and standard error for marginal mean parameters for the OMTM were similar to those for the IOMTM(1) and IOMTM(2). To compare the fit of the models, in particular, the dependence structure, we computed the AIC. The AIC for OMTM was 3800.700 and for IOMTM(1)-1 3876.306, indicating that IOMTM(1)-1 fit better than OMTM. Comparison of deviances for IOMTM(1)-1, IOMTM(1)-2, and IOMTM(1)-3 which are nested yields $\triangle D_{12}^{(1)} = 2 \times (1924.153 - 1916.225) = 15.856$, $p-$value= 0.015 on 6 d.f and $\triangle D_{13}^{(1)} = 2 \times (1924.153 - 1916.690) = 14.926$, $p-$value= 0.246 on 12 d.f. The AIC's for IOMTM(1)-2 and IOMTM(1)-3 which were not nested were 3872.450 and 3885.380, respectively. These comparisons indicated that IOMTM(1)-2 was the better fitting model among IOMTM(1)'s and OMTM. Similarly, we had IOMTM(2)-2 as better fitting among IOMTM(2)'s by comparison of deviances and the AIC's ($\triangle D_{12}^{(2)} = 22.156$, $p-$value= 0.036 on 12 d.f.; $\triangle D_{13}^{(2)} = 15.123$, $p-$value= 0.917 on 24 d.f.; AIC for IOMTM(2)-2=3825.910, AIC for IOMTM(2)-3=3861.820). Again, we compared de-

viances for IOMTM(1)-2 and IOMTM(2)-2 ($\triangle D_{22} = 54.540$, p−value< 0.0001 on 12 d.f.) and concluded that IOMTM(2)-2 was the best fitting model.

4.1.1 Graphical assessment of the dependence model   Figure 1 presents conditional probabilities given previous values for the OMTM(1) given in (8). We arbitrarily chose one subject and visit because the shapes of conditional probabilities are the same across subjects (the intercepts $\triangle_{itk}$ only shift the trajectories up or down). The trajectories of conditional probabilities change quadratically with previous responses. Thus, the quadratic model given in (9) appears adequate to explain the change in the conditional probabilities as a function of the previous response. We were unable to get an OMTM(2) to converge to obtain a similar plot for first and second order dependence.

4.1.2 Inference on regression coefficients   In the IOMTM(2)-2, the β coefficient of Visit*Arm2 was significant with an estimate of -1.847 and SE of 0.874. This indicated that the level of fatigue increased over time on the IROX arm and this was significantly greater than for patients on the IFL (control) arm. The β coefficient of Visit*Arm1 was not significant. This indicated that the level of fatigue did not change over time on FOLFOX arm and there was no significant difference of fatigue over time between the IFL and the FOLFOX arms. The cumulative probabilities for the IROX arm decreased more steeply over time compared with the FOLFOX arm and the IFL arm. Thus, for this particular measure of QOL, fatigue, the worst treatment was not the one that provided the longest time to progression and best overall survival (FOLFOX).

4.2   *Dropout due to progression/death*

A large number of subjects dropped out due to tumor progression or death (40.5%). Thus, the analysis in Section 4.1 is problematic as among other things, it implicitly

imputes missing values for the dropouts due to death. Imputing such values for subjects who died is not a sensible approach. We would argue for QOL data, that imputing these QOL values for those who dropped out due to their disease progressing is not sensible either.

Table 3 summarizes the reasons for dropout in the three treatment arms. The dropout rates due to progression/death were marginally higher in IFL and IROX arms. To deal with events due to progression/death, we used a mixture model for the joint distribution of longitudinal measures and progression/death times (Hogan and Laird, 1997) similar to previous work by Pauler et al. (2003) and Kurland and Heagerty (2005). For this dataset, we had the actual progression/death times for subjects who dropped out due to progression/death and also for those who dropped out for other reasons. Table 4 summarizes the visit window in which patients progressed/died for all three treatments. Note, for some subjects, this is past the time they actually dropped out.

Define S to be the progression/death time. We specify the ordinal MTM models conditional on progression/death time, S. Due to the small sample sizes when conditioning on individual times, we assumed the parameters were the same for $S = 1, \ldots, 5$ (those who progressed/died before the end of the study) but different for those who did not, $S = 6$. This approach implicitly assumes that for a given progression/death time (pattern), that missing data before the progression/death time is MAR (conditional on pattern); this situation occurs if dropout is not due to progression/death.

Within this framework, the probability of fatigue for patients who progressed/died beyond time k is given by

$$P(Y_t > c|S > k, \text{Tx}) = \frac{\sum_{j>k} P(Y_t > c|S = j, \text{Tx})P(S = j|\text{Tx})}{\sum_{j>k} P(S = j|\text{Tx})}. \qquad (11)$$

where Tx is treatment and $P(Y_t > c \mid S = j, \text{Tx})$ is only defined for $t < j$. In our analysis here, our target probabilities are (11) evaluated at $k = 5$; i.e., those who did

not progress/die before the end of the study. Table 5 presents the estimated target probabilities on the three treatment arms. The probabilities of high fatigue for IROX and FOLFOX arm increased over time, whereas that for IFL arm was more stable. However, there were no significant differences between the treatment arms. Thus, we conclude that patients' fatigue was not affected by treatment unlike in the models under MAR.

5.   Conclusions and discussion

We proposed two marginalized transition models for longitudinal ordinal data that directly model marginal probabilities as function of covariates while accounting for the longitudinal correlation via a Markov structure. The IOMTM has fewer dependence parameters than the OMTM and exploits the ordering of previous responses. Parameter estimation was based on maximum likelihood using a Fisher-scoring method. We showed that the ML estimates for the (I)OMTM(1) were consistent regardless of specification of (8) when there was no missing data. Simulation studies indicated that marginal mean parameter estimates were robust to the dependence model being incorrectly specified in (I)OMTM(1)'s under MAR dropout. However, IOMTM(2)'s were much less robust to dependence model mis-specification under MAR dropout.

Calculations and analyses in this paper are based on 1st and 2nd order (I)OMTMs. Extension to higher orders is also possible. However, such models introduce more dependence parameters and more complex computing and constraints; such models are workable for larger datasets. An alternative formulation would be to introduce random effects instead of, or in addition to, previous response to model the longitudinal dependence. This is ongoing work.

As discussed in Section 4, about 40% of the patients dropped out due to tumor progression or death. We adjusted for this using a pattern mixture approach with patterns defined based on the observed progression/death times. To obtain the causal effect of treatment

while accounting for progression/death, a principal stratification approach (Frangakis and Rubin, 2002) could be developed which would condition on progressing/dying past a given time on all three treatment arms. This is also ongoing work.

In (5), we specified a very general formulation for pth order Markov dependence and then simplified it to an additive structure with quadratics for the individual components. Using the more general formulation is possible and would allow for more flexible dependence; for example, removing the additive restriction and allowing interactions. Computationally, this would create no additional burden. We are currently exploring such generalizations.

6. Supplementary Materials

Web Appendices, detailed calculations, Tables, and Figures referenced in Section 3, are available under the Paper Information link at the Biometrics website http://www.tibs.org/biometrics.

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Table 1

Bias of IOMTM(1) maximum likelihood estimators when data are missing at random (MAR). Displayed is the average regression coefficient estimates and the percent relative bias, $100 \times (\hat{\beta} - \beta)/\beta$

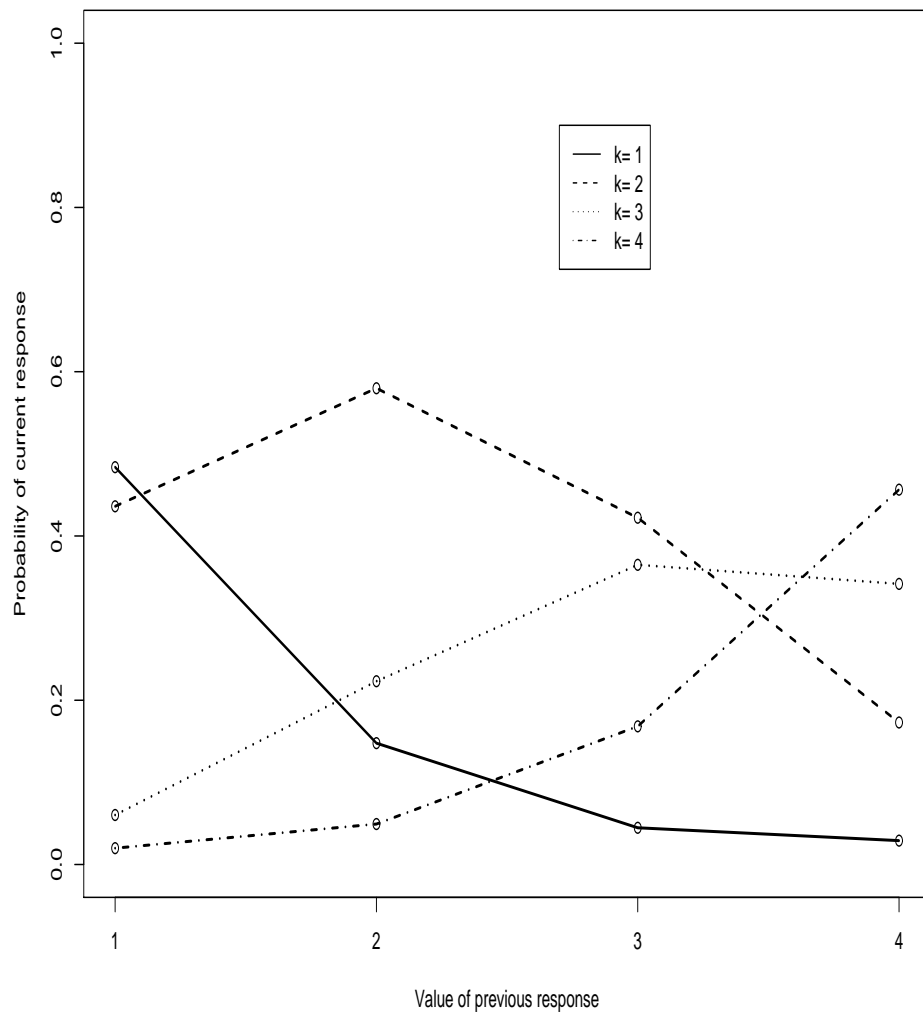| Unstructured Marginal mean				Structured Marginal mean			
para.	truth	mean	bias(%)	truth	para.	mean	bias(%)
int1	-1.00	-1.00	0.0	int1	-1.00	-1.00	0.0
int2	0.70	0.70	0.0	int2	0.70	0.70	0.0
int3	2.00	2.01	0.5	int3	2.00	2.00	0.0
grp1	0.10	0.10	0.0	grp1	0.10	0.10	0.0
grp2	-0.50	-0.50	0.0	grp2	-0.50	-0.50	0.0
vis1	0.10	0.10	0.0	vis	-0.50	-0.49	-2.0
vis2	-1.50	-1.51	0.7				
vis3	1.20	1.20	0.0				
vis4	-0.40	-0.39	-2.5				
vis5	0.80	0.80	0.0				
vis6	-0.30	-0.29	-3.3				
vis7	-1.00	-1.03	3.0				

Figure 1. Conditional probabilities for category k given previous response under OMTM(1).

Table 2

Maximum likelihood estimates for OMTM and IOMTM

	IOMTM(1)-1	IOMTM(1)-2	IOMTM(1)-3	IOMTM(2)-1	IOMTM(2)-2	IOMTM(2)-3	OMTM
Marg. para.	Coef. (SE)	Coef. (SE)	Coef. (SE)	Coef. (SE)	Coef. (SE)	Coef. (SE)	Coef. (SE)
Intercept 1	-1.099^* (0.124)	-1.094^* (0.122)	-1.104^* (0.124)	-1.082^* (0.123)	-1.084^* (0.121)	-1.095^* (0.123)	-1.099^* (0.124)
Intercept 2	0.844^* (0.121)	0.841^* (0.120)	0.836^* (0.119)	0.849^* (0.120)	0.841^* (0.117)	0.832^* (0.119)	0.844^* (0.121)
Intercept 3	2.318^* (0.143)	2.316^* (0.142)	2.301^* (0.142)	2.319^* (0.143)	2.317^* (0.141)	2.293^* (0.143)	2.319^* (0.143)
Visit	-0.290 (0.675)	-0.427 (0.683)	-0.235 (0.678)	-0.455 (0.617)	-0.484 (0.600)	-0.124 (0.651)	-0.265 (0.676)
Arm1	-0.066 (0.167)	-0.070 (0.164)	-0.060 (0.166)	-0.086 (0.164)	-0.088 (0.161)	-0.070 (0.164)	-0.065 (0.167)
Arm2	0.036 (0.165)	0.036 (0.163)	0.043 (0.165)	0.025 (0.163)	0.055 (0.160)	0.036 (0.162)	0.037 (0.166)
Visit*Arm1	-0.647 (1.013)	-0.458 (1.027)	-0.767 (1.006)	-0.346 (0.926)	-0.160 (0.906)	-0.815 (0.937)	-0.687 (1.014)
Visit*Arm2	-1.593 (0.985)	-1.579 (0.996)	-1.637 (0.984)	-1.507 (0.897)	-1.847^* (0.874)	-1.835 (0.888)	-1.606 (0.986)
Max. loglike.	-1924.153	-1916.225	-1916.690	-1900.033	-1888.955	-1886.910	-1923.350
AIC	3876.306	3872.450	3885.380	3840.660	3825.910	3861.820	3880.700

* indicates significance under 95% confidence level

Table 3

Completers and dropouts by treatment groups. Proportions in parentheses

| Treatment | Completer | Reason for dropout | | Total |
		Progression/Death	Other	
IFL	10 (0.043)	117 (0.498)	108 (0.460)	235
FOLFOX	4 (0.017)	68 (0.292)	161 (0.691)	233
IROX	4 (0.017)	101 (0.423)	134 (0.561)	239
Total	18 (0.025)	286 (0.405)	403 (0.570)	707

Table 4

Progression/Death windows by treatment groups. Proportions in parentheses

| Treatment | Progression/Death window | | | | | | Total |
	1	2	3	4	5	6[1]	
IFL	35(0.149)	32(0.136)	38(0.162)	26(0.111)	18(0.077)	86(0.366)	235
FOLFOX	16(0.069)	28(0.120)	24(0.103)	17(0.073)	19(0.082)	129(0.554)	233
IROX	22(0.092)	33(0.138)	36(0.151)	27(0.113)	16(0.067)	105(0.439)	239
Total	73(0.103)	93(0.132)	98(0.139)	70(0.099)	53(0.075)	320(0.453)	707

[1]Window 6 means 'after study.'

Table 5

Maximum Likelihood Estimates of $P(Y_t > c | S > 5, Tx)$ (and standard errors) where S is progression/death time.

Tx	c	Visit(t) 1	2	3	4	5	6
IFL	1	0.756	0.754	0.752	0.751	0.749	0.747
		(0.037)	(0.033)	(0.037)	(0.047)	(0.060)	(0.075)
	2	0.281	0.279	0.277	0.275	0.273	0.271
		(0.039)	(0.025)	(0.039)	(0.050)	(0.063)	(0.078)
	3	0.076	0.076	0.075	0.074	0.074	0.073
		(0.017)	(0.016)	(0.017)	(0.020)	(0.024)	(0.028)
FOLFOX	1	0.744	0.759	0.773	0.786	0.799	0.811
		(0.032)	(0.028)	(0.034)	(0.044)	(0.055)	(0.066)
	2	0.268	0.284	0.300	0.316	0.333	0.351
		(0.032)	(0.030)	(0.039)	(0.055)	(0.075)	(0.097)
	3	0.072	0.077	0.083	0.089	0.096	0.103
		(0.014)	(0.014)	(0.018)	(0.024)	(0.031)	(0.041)
IROX	1	0.741	0.761	0.779	0.797	0.813	0.829
		(0.035)	(0.030)	(0.035)	(0.044)	(0.053)	(0.062)
	2	0.265	0.286	0.308	0.330	0.354	0.378
		(0.034)	(0.032)	(0.042)	(0.058)	(0.079)	(0.102)
	3	0.071	0.078	0.086	0.095	0.104	0.114
		(0.015)	(0.015)	(0.019)	(0.025)	(0.035)	(0.046)