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Latent drop-out based transitions in linear quantile hidden Markov models for longitudinal responses with attrition

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Abstract Longitudinal data are characterized by the dependence between observations from the same individual. In a regression perspective, such a dependence can be usefully ascribed to unobserved features (covariates) specific to each individual. On these grounds, random parameter models with time-constant or time-varying structure are now well established in the generalized linear model context. In the quantile regression framework, specifications based on random parameters have only recently known a flowering interest. We start from the recent proposal by Farcomeni (2012) on longitudinal quantile hidden Markov models, and extend it to handle potentially informative missing data mechanisms. In particular, we focus on monotone missingness which may lead to selection bias and, therefore, to unreliable inferences on model parameters. We detail the proposed approach by re-analyzing a well known dataset on the dynamics of CD4 cell counts in HIV seroconverters and by means of a simulation study.

Keywords Quantile regression · longitudinal data · hidden Markov models · latent drop-out classes

1 Introduction

Quantile regression has become a standard tool to model the distribution of a continuous response variable as a function of a set of observed covariates. When the interest lies not only on the center of the response distribution

and/or when the observed data may include some outliers, quantile regression represents an interesting alternative to standard mean regression. During the last few years, the basic homogeneous quantile regression model (Koenker and Bassett, 1978) has been extended to deal with longitudinal responses. To handle the dependence between measurements taken over time on the same individual, unit-specific, time-constant, random parameters can be added to the model specification (as in Geraci and Bottai, 2007; Liu and Bottai, 2009; Geraci and Bottai, 2014). A potential alternative is to consider time-varying random parameters. In this perspective, by extending standard hidden Markov models (Wiggins, 1973), Farcomeni (2012) proposes a linear quantile model with a random intercept that varies over time according to a first-order hidden Markov chain. For a general treatment of hidden Markov models (HMMs) for longitudinal data see Bartolucci et al (2013). A review of quantile regression models for repeated observations is provided by Marino and Farcomeni (2015).

A common feature of longitudinal studies is that individuals may leave the study before its end. Thus, incomplete individual sequences represent a further challenge, since not all individuals have the same weight in building up the log-likelihood function. A major problem is the so-called informative missingness: once conditioning on the observed covariates and responses, the selection of units in the study may still depend on future, unmeasured, responses. When ignored, this missing data generating mechanism may severely bias parameter estimates and lead to misleading conclusions. Following the proposals by Roy (2003) and Roy and Daniels (2008), we consider a pattern mixture representation (Little and Wang, 1993) and develop a linear quantile hidden Markov model with latent drop-out classes. The idea behind such a model is that, after conditioning on the observed covariates, differences between sample units arise due to unobserved heterogeneity. Time-varying random parameters with Markovian structure capture differences related to the dynamics of omitted covariates. A further source of unobserved heterogeneity may be due to individuals having a different propensity to drop-out from the study. These sub-populations are identified by adding in the model a latent multinomial variable, whose ordered categories directly influence the Markov transition matrix.

The paper is structured as follows: in section 2, the linear quantile hidden Markov model is briefly reviewed. In section 3, we extend this proposal in a pattern mixture perspective, by considering latent drop-out classes to capture individual-specific propensities to leave the study. The modified EM algorithm

for parameter estimation is discussed in section 4; the proposed method is applied in section 5 to a well-known benchmark multi-center longitudinal study on the time progression of CD4 cell numbers in HIV seroconverters. Section 6 discusses the results of a simulation study. Last section contains concluding remarks and outlines potential, future, research lines.

2 Linear quantile hidden Markov models

Let us suppose a longitudinal study collects repeated measures of a *continuous* response variable Y_{it} on a sample of $i = 1, \ldots, n$ subjects at time occasions $t = 1, \ldots, T$. To account for dependence between measurements on the same statistical unit, a standard approach is to specify a conditional model for the responses, which are assumed to be independent conditional on a set of individual-specific latent variables. In the context of generalized linear models for longitudinal responses, such latent effects may be either time-constant, as in mixed effect models (Laird and Ware, 1982), or time-varying, as in hidden Markov models (Wiggins, 1973). For a combination of both, see Altman (2007) and Maruotti (2011). While this class of models has quite a long history in the generalized linear model framework, only recently its scope has been broadened to quantile regression, see Geraci and Bottai (2007, 2014) and Liu and Bottai (2009). Models with time-varying parameters have been introduced by Farcomeni (2012) to model the (conditional) quantiles of a longitudinal response. This proposal (in the following lqHMM) is based on the existence of two related processes: a latent process with a Markov structure and an observed measurement process, whose parameters are defined by the current state of the hidden Markov chain. Conditional on the state occupied at a given time occasion, the longitudinal observations from the same individual are assumed to be independent (local independence assumption).

Let us consider a quantile $\tau \in (0, 1)$, and denote by $S_{it}(\tau)$ a quantile-specific, homogeneous, first order, hidden Markov chain. The chain takes values in the finite set $\mathcal{S}(\tau) = \{1, \ldots, m(\tau)\}$; $\boldsymbol{\delta}(\tau)$ and $\mathbf{Q}(\tau)$ are the initial probability vector and the transition probability matrix of the chain, respectively. The lqHMM can be specified as follows:

$$\begin{aligned} Y_{it} \mid s_{it} &\sim \text{ALD}(\mu_{it}(s_{it}, \tau), \sigma(\tau), \tau) \\ \mu_{it}(s_{it}, \tau) &= \alpha(s_{it}, \tau) + \mathbf{x}'_{it}\boldsymbol{\beta}(\tau) \end{aligned} \tag{1}$$

where μ, σ and τ are the location, the dispersion and the skewness parameters for the asymmetric Laplace distribution. The location parameter is linear in the time-varying intercept, $\alpha(s_{it}, \tau)$, and in the vector of fixed effects $\boldsymbol{\beta}(\tau)$. The assumption that the response variable has an asymmetric Laplace distribution, see Geraci and Bottai (2007), is made to recast standard quantile loss optimization within a maximum likelihood framework. Moving from the random intercept to a more general random coefficient model, we may write

$$\mu_{it}\left(s_{it}, \tau\right) = \mathbf{x}_{it}'\boldsymbol{\beta}(\tau) + \mathbf{z}_{it}'\boldsymbol{\alpha}(s_{it}, \tau)$$

where $\boldsymbol{\beta}(\tau)$ summarizes the fixed effect of observed covariates on the τ-th (conditional) quantile of the response distribution, while $\boldsymbol{\alpha}(s_{it}, \tau)$ represents the individual-specific effects associated to a subset of $\mathbf{x}_{it}$ for an individual in state s_{it} at time occasion t. Based on such modelling assumptions, the individual contribution to the observed data likelihood can be written as follows:

$$f_Y(\mathbf{y}_i) = \sum_{\mathbf{s}_i} f_{Y|S}(\mathbf{y}_i \mid \mathbf{s}_i) f_S(\mathbf{s}_i) \tag{2}$$

Obviously, this framework leads to quite a general structure of association between longitudinal measurements. However, this model can not properly handle incomplete sequences in the presence of an informative missing data process (Little and Rubin, 2002). In the next section, we extend the current model specification to account for individual differences in the propensity to leave the study.

3 Handling informative missingness

Let us consider a measurement process affected by monotone missingness: for each unit $i = 1, \ldots, n$, the measurements are available at time points $t = 1, \ldots, T_i$ only, with $T_i \leq T$. Let us denote by R_{it} the missing data indicator variable, which is equal to 1 if the i-th subject is not available at the t-th occasion. Since we consider monotone missingness, $R_{it} = 1 \Rightarrow R_{it'} = 1$, $t' \geq t = 1, \ldots, T$. When the drop-out is informative, the missing data process needs to be properly modelled to reduce the risk of obtaining unreliable parameter estimates. The drop-out is defined to be informative when, conditional on observed responses and covariates, the missing data process still depends on the current, unobserved, values and/or when parameter distinctiveness between the distribution of Y and R does not hold; Little and Rubin (2002) give a general treatment of this topic.

In these cases, a more general model should be defined. In the quantile regression framework, few attempts have been made to handle informative missingness. Lipsitz et al (1997) and Yi and He (2009) suggest a GEE approach (Liang and Zeger, 1986), while Farcomeni and Viviani (2015) consider a joint model (JM) representation, see Rizopoulos (2012). While this latter approach is an elegant way to handle dependence between longitudinal responses and missingness, JMs require the distribution for the missing data process to be completely specified and this often represents a delicate matter. Here, we focus on PMMS (PMMs), see Little and Wang (1993). The rationale for this class of models is that each subject has his/her own propensity to drop-out from the study. Individuals with similar propensities share some common observed/unobserved features and the model for the longitudinal response is given by a mixture over these patterns. PMMs do not need the distribution of the missing data generating process to be specified, but, as a drawback, they are often overparameterized. This issue may be (at least potentially) solved by defining appropriate identifying restrictions. Latent drop-out (LDO) models (Roy, 2003; Roy and Daniels, 2008) represent a potential step in this direction. Here, a limited number of LDO classes is considered and units belonging to the same class are assumed to share common unobserved characteristics; these influence, either directly or indirectly, the response variable distribution. To explain our proposal, let $\boldsymbol{\zeta}_i(\tau) = (\zeta_{i1}(\tau), ..., \zeta_{iG}(\tau))$ be a (quantile-specific) multinomial random variable with component $\zeta_{ig}(\tau) = 1$ if subject i belongs to the g-th LDO class and zero otherwise. These categories represent ordered propensities to drop-out; that is, we assume that, for $g > g'$, units with $\zeta_{ig}(\tau) = 1$ have a lower propensity to leave the study than units with $\zeta_{ig'}(\tau) = 1$. For a generic quantile $\tau \in (0, 1)$, the ordering is specified through the following model:

$$\Pr\left(\sum_{l=1}^{g} \zeta_{il}(\tau) = 1 \mid T_i\right) = \frac{\exp\{\lambda_{0g}(\tau) + \lambda_1(\tau)\, T_i\}}{1 + \exp\{\lambda_{0g}(\tau) + \lambda_1(\tau)\, T_i\}}. \tag{3}$$

under the constraint $\lambda_{0g}(\tau) \leq \lambda_{0g'}(\tau)$ if $g < g'$. The probability of belonging to one of the first g classes is, thus, modelled as a monotone function of the time to drop-out; the probability of a specific class is obtained as the difference between two adjacent cumulative logits (Agresti, 2010). We prefer the proportional-odds specification used in Roy and Daniels (2008) over the non-proportional-odds discussed by Roy (2003) since the common slope and the constraints above imply that the distribution of $\boldsymbol{\zeta}_i(\tau)$ at different values of T_i is stochastically ordered. We assume that the latent drop-out class variable sum-

marizes all the dependence between the longitudinal response and the missing data mechanism. That is, conditional on the LDO class, the two processes are independent. As it is obvious, LDO classes may influence the response variable distribution in several ways: for example, they may produce class-specific changes to the fixed effect parameter vector, as in Marino et al (2015). Alternatively, they may produce changes in the locations of the hidden Markov chain, thus giving rise to a LDO-specific support for the time-varying random parameters. Here, we discuss a further alternative; we assume that each LDO class corresponds to a different matrix of transition probabilities. That is, we consider a (quantile-specific) homogeneous, first order, hidden Markov chain, $S_{it}(\tau)$, taking values in the finite set $\mathcal{S}(\tau) = \{1, \ldots, m(\tau)\}$. The corresponding initial probability vector is assumed to be constant among LDO classes and is denoted by $\boldsymbol{\delta}(\tau)$, while the transition probability matrix $\mathbf{Q}(g; \tau)$ is specific to each LDO class, $g = 1, \ldots, G$. This approach shares some features with the proposal by Maruotti and Rocci (2012), where latent class-specific transitions are considered in the framework of standard HMMs. As it is clear, the proposed specification covers a range of situations which is more general than a simple change in the location parameters of the hidden Markov chain. By allowing $\mathbf{Q}(\cdot)$ depend on g, we may define states that are "visited" only by individuals in a given LDO class, leading to latent class-specific parameter values. The proposed model is in line with Bartolucci and Farcomeni (2015) and Maruotti (2015), where standard HMMs are extended to deal with informative drop-outs. More in detail, Bartolucci and Farcomeni (2015) discuss a shared parameter model with time-constant and time-varying (discrete) random intercepts shared by the longitudinal and the missing data process. Maruotti (2015) describes a pattern mixture approach with the Markov transition matrix being a function of the time to drop-out. When compared with the former, our proposal does not need the distribution of the missing data process to be specified, thus avoiding unverifiable parametric assumptions. When compared with the latter, our approach seems to be more general and offer greater flexibility. Finally, it is worth noticing that the model we propose reduces to the lqHMM specification when a single LDO class ($G = 1$) is considered.

Let $\boldsymbol{\Psi}(\tau) = (\boldsymbol{\theta}(\tau), \sigma(\tau), \boldsymbol{\delta}(\tau), \mathbf{Q}(\tau), \boldsymbol{\lambda}(\tau))$, where $\boldsymbol{\theta}(\tau) = (\boldsymbol{\beta}(\tau), \boldsymbol{\alpha}_1(\tau), \ldots, \boldsymbol{\alpha}_{m(\tau)}(\tau))$ denotes the vector of longitudinal model parameters, and let $\boldsymbol{\Phi}(\tau)$ be the vector of parameters indexing the distribution of the time to drop-out, $f_T(T_i \mid \boldsymbol{\Phi}; \tau)$. Based on the previous modelling assumptions, the observed individual likelihood for a generic unit is obtained by marginalizing the joint distribution of observed and latent variables over the hidden Markov chain and

the LDO class indicator. Suppressing the dependence on model parameters to simplify the notation, the following expression holds:

$$f_{YT}(\mathbf{y}_i, T_i; \tau) = \sum_{\mathbf{s}_i\, \boldsymbol{\zeta}_i} f_{Y|S\zeta}(\mathbf{y}_i \mid \mathbf{s}_i, \boldsymbol{\zeta}_i; \tau) f_S(\mathbf{s}_i \mid \boldsymbol{\zeta}_i; \tau) f_{\zeta|T}(\boldsymbol{\zeta}_i \mid T_i; \tau) f_T(T_i; \tau). \tag{4}$$

From the equation above, it is clear that the marginal distribution of the time to drop-out can be left unspecified and ignored when maximizing the likelihood with respect to $\boldsymbol{\Psi}(\tau)$; inference may be based on the conditional distribution $f_{Y|T}(\mathbf{y}_i \mid T_i; \tau)$ only.

4 Parameter estimation

The general structure of the EM algorithm (Dempster et al, 1977) we use for parameter estimation can be sketched as follows. To keep the notation simple, we will omit the dependence of model parameters on the specific quantile τ we consider. Let $u_{it}(h) = I(S_{it} = h)$ be the variable indicating the i-th unit is in the h-th hidden state at occasion t and let $u_{it}(h, k)$ be the indicator variable for the i-th unit moving from the h-th state at occasion $t-1$ to the k-th one at t. Last, let ζ_{ig} be the indicator variable for unit $i = 1, \ldots, n$ in the g-th LDO class. For a given quantile τ, the (conditional) log-likelihood for complete data is

$$\begin{aligned}\ell_c(\boldsymbol{\Psi}) = \sum_{i=1}^{n} \Bigg\{ &\sum_{h=1}^{m} u_{i1}(h) \log \delta_h + \sum_{t=2}^{T_i} \sum_{h=1}^{m} \sum_{k=1}^{m} \sum_{g=1}^{G} u_{it}(k, h) \zeta_{ig} \log q_{kh}(g) + \\ &+ \sum_{g=1}^{G} \zeta_{ig} \log \pi_g - T_i \log \sigma - \sum_{t=1}^{T_i} \sum_{h=1}^{m} u_{it}(h) \rho_\tau \left(\frac{y_{it} - \mu_{it}(S_{it} = h)}{\sigma} \right) \Bigg\}\end{aligned} \tag{5}$$

The E-step of the algorithm requires the computation of the expected values for the indicator variables $u_{it}(h), u_{it}(h, k)$ and ζ_{ig}, conditional on the observed data and the current parameter estimates. As it is usual with hidden Markov models, computation is simplified by considering the forward and the backward variables (Baum et al, 1970). In the present framework, forward variables, $a_{it}(h, g)$, define the joint density of the longitudinal measures up to occasion t and the h-th state at t, for a generic individual in the g-th LDO class:

$$a_{it}(h, g) = f\left[y_{i1:t}, S_{it} = h \mid \zeta_{ig} = 1\right]. \tag{6}$$

Following Baum et al (1970), these terms can be computed recursively as

$$a_{i1}(h,g) = \delta_h f_{Y|S}\big[y_{i1} \mid S_{i1} = h\big], \tag{7}$$
$$a_{it}(h,g) = \sum_{k=1}^{m} a_{it-1}(k,g) q_{kh}(g) f_{Y|S}\big[y_{it} \mid S_{it} = h\big].$$

Similarly, the backward variables, $b_{it}(h,g)$, represent the probability of the longitudinal sequence from occasion $t+1$ to the last observation, conditional on being in the g-th LDO class and in the h-th state at t:

$$b_{it}(h,g) = f\big[y_{it+1:T_i} \mid S_{it} = h, \zeta_{ig} = 1\big]. \tag{8}$$

Also backward variables can be derived recursively:

$$b_{iT_i}(h,g) = 1, \tag{9}$$
$$b_{it-1}(h,g) = \sum_{k=1}^{m} b_{it}(k,g) q_{hk}(g) f_{y|sb}\big[y_{it} \mid S_{it} = h\big],$$

For a detailed description of the Baum-Welch algorithm, see the seminal paper by Baum et al (1970) and the reference monograph by Zucchini and MacDonald (2009).

Computation of the expected complete data log-likelihood, conditional on the observed data and the current parameter estimates, leads to

$$Q(\boldsymbol{\Psi} \mid \hat{\boldsymbol{\Psi}}) = \sum_{i=1}^{n} \Bigg\{ \sum_{h=1}^{m} \hat{u}_{i1}(h) \log \delta_h + \sum_{t=2}^{T_i} \sum_{h,k=1}^{m} \sum_{g=1}^{G} \hat{\zeta}_{ig} \hat{u}_{it}(k,h \mid g) \log q_{kh}(g) +$$
$$+ \sum_{g=1}^{G} \hat{\zeta}_{ig} \log \pi_g - T_i \log(\sigma) - \sum_{t=1}^{T_i} \sum_{h=1}^{m} \sum_{g=1}^{G} \Big[\hat{u}_{it}(h) \rho_\tau \left(\frac{y_{it} - \mu_{it}(S_{it} = h)}{\sigma} \right) \Bigg\}, \tag{10}$$

where $\hat{u}_{it}(h)$ and $\hat{\zeta}_{ig}$ represent the posterior expectation of the indicator variables we have previously introduced. Moreover, $\hat{u}_{it}(k,h \mid g)$ denotes the posterior probability for the i-th unit who is in state k at occasion $t-1$ and moves to state h at occasion t, given she/he belongs to the g-th LDO class. These posterior probabilities can be easily obtained by exploiting the forward and backward variables (7) and (9) as:

$$\hat{u}_{it}(h) = \frac{\sum_g a_{it}(h,g) b_{it}(h,g) \pi_g}{\sum_h \sum_g a_{it}(h,g) b_{it}(h,g) \pi_g}$$

$$\hat{u}_{it}(k,h \mid g) = \frac{a_{it-1}(k,g) q_{kh}(g)\, f_{s|s}\left(y_{it} \mid S_{it}=h,\right) b_{it}(h,g)}{\sum_h \sum_k a_{it-1}(k,g) q_{kh}(g)\, f_{Y|S}\left(y_{it} \mid S_{it}=h,\right) b_{it}(h,g)}.$$

$$\hat{\zeta}_{ig} = \frac{\sum_h a_{iT_i}(h,g)\pi_g}{\sum_g \sum_h a_{iT_i}(h,g)\pi_g}$$

The M-step of the EM algorithm require the maximization of the $Q(\cdot)$ function with respect to model parameters. Closed form solutions are available for the parameters of the hidden Markov process:

$$\hat{\delta}_h = \frac{\sum_{i=1}^n \hat{u}_{i1}(h)}{n}, \quad \hat{q}_{kh}(g) = \frac{\sum_{i=1}^n \sum_{t=1}^{T_i} \hat{u}_{it}(k,h \mid g)}{\sum_{i=1}^n \sum_{t=1}^{T_i} \sum_{h=1}^m \hat{u}_{it}(k,h \mid g)} \tag{11}$$

The estimated of the scale parameter for the longitudinal response is

$$\hat{\sigma} = \frac{1}{\sum_{i=1}^n T_i} \sum_{t=1}^{T_i} \sum_{h=1}^{m} \hat{u}_{it}(h) \rho_\tau \left(y_{it} - \hat{\mu}_{it}(S_{it}=h)\right). \tag{12}$$

Parameters in the longitudinal and in the LDO class model, $(\boldsymbol{\theta}, \boldsymbol{\lambda})$, are estimated by finding the zeros of weighted score functions. For the longitudinal outcome, weights are given by the posterior probabilities of the hidden states, $\hat{u}_{it}(h)$. The corresponding estimating equation is

$$\sum_{i=1}^{n} \sum_{t=1}^{T_i} \sum_{h=1}^{m} \hat{u}_{it}(h) \frac{\partial}{\partial \boldsymbol{\theta}} \left[\rho_\tau \left(\frac{y_{it} - \mu_{it}(s_{it})}{\hat{\sigma}} \right) \right] = \mathbf{0}, \tag{13}$$

For the latent drop-out model, the weights are given by the LDO class posterior probabilities, $\hat{\zeta}_{ig}$, and lead to the estimating equation

$$\sum_{i=1}^{n} \sum_{g=1}^{G-1} \hat{\zeta}_{ig} \frac{\partial}{\partial \boldsymbol{\lambda}} \left\{ \log \left[\left(\frac{e^{\lambda_{0g} + \lambda_1 T_i}}{1 + e^{\lambda_{0g} + \lambda_1 T_i}} \right) - \left(\frac{e^{\lambda_{0g-1} + \lambda_1 T_i}}{1 + e^{\lambda_{0g-1} + \lambda_1 T_i}} \right) \right] \right\} = \mathbf{0} \tag{14}$$

The E- and the M- steps are repeatedly alternated until convergence, that is until the following condition holds

$$\ell^{(r+1)} - \ell^{(r)} < \epsilon,$$

for a fixed constant $\epsilon > 0$. The algorithm reaches convergence for a given number of hidden states, m, and of LDO classes, G, which we consider fixed and known. For a given combination $[m, G]$, several starting points are used to avoid local maxima. As a result, we have a set of possible solutions, and the final $[m, G]$-based estimates come from the model with the highest log-

likelihood value obtained over the set of starting points considered. As it typically happens in the linear quantile mixed model framework, standard errors for parameter estimates are derived by exploiting a non-parametric block bootstrap (see eg Buchinsky, 1995). Bootstrap samples are obtained by sampling individuals and retaining the corresponding longitudinal sequence to preserve the within individual dependence structure.

5 Real data example: CD4 data

To explore the empirical behaviour of the model, we re-consider the CD4 cell count data discussed, among others, by Zeger and Diggle (1994). These data come from the Multicenter AIDS cohort study (MACS) conducted since 1984 with the aim at analysing HIV progression over time (for a detailed discussion of the study, see Kaslow et al, 1987). It includes nearly 5000 gay and bisexual men from Baltimore, Pittsburgh, Chicago and Los Angeles. As it is well known, one of the effects of HIV is the reduction of T-lymphocytes, referred to as CD4 cells, which play a vital role in immune function; the virus progression can, therefore, be assessed by measuring the number of CD4 cells over time.

The analysed dataset entails 2376 repeated measurements coming from 369 men who were seronegative at the beginning of the study and seroconverted during the analysed time window. They have been observed from 3 years before up to 6 years after the seroconversion: each individual has been followed from a minimum of 1 to a maximum of 12 occasions. While the time occasions are not equally spaced, the distribution of the time elapsed between successive visits is concentrated around 0.50 (that is, half a year) and, therefore, we may consider occasions as if they were equally spaced. This greatly simplifies notation and estimation. At each visit, the level of T-lymphocytes in the blood has been measured together with a number of covariates: years since seroconversion (negative values indicate that the current CD4 measurement has been taken before the seroconversion), age at seroconversion (centered around 30), smoking (packs per day), recreational drug use (yes or no), number of sexual partners, depression symptoms as measured by the CESD scale (larger values indicate more severe symptoms). The response is defined by the log transformed CD4 counts, that is log(1+CD4 count).

As it is often the case with longitudinal designs, some of the units in the sample leave the study before its ending and thus present incomplete information. In table 1, we report the number of individuals available at each visit;

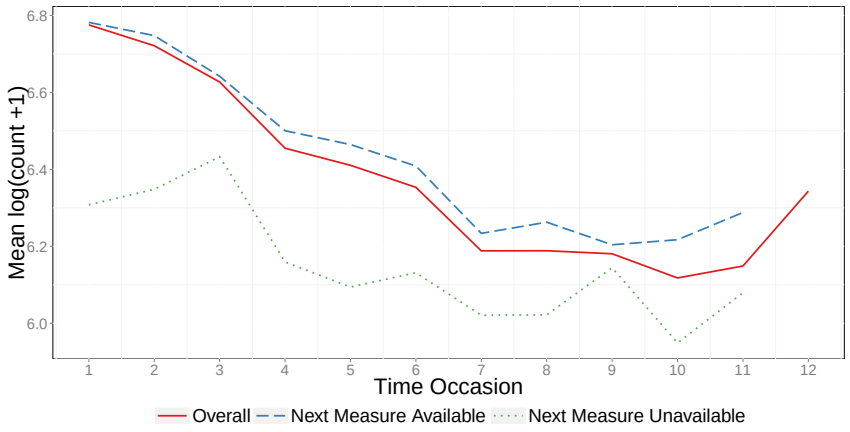
as it can be seen, only a small number of individuals presents complete data records.

Table 1: CD4 data. Number of individuals in the study at each time occasion.

Visit	1	2	3	4	5	6	7	8	9	10	11	12
	369	364	340	315	268	225	173	133	92	54	33	10

Figure 1 displays the mean response evolution during the follow up, for the overall sample and for the sample stratified by whether or not units drop-out from the study between the current and the subsequent time occasion. As it may be noticed, a progressive decrease in the CD4 counts is observed, which is coherent with the progression of the virus. However, some differences between

Fig. 1: CD4 data. Response variable distribution at each time occasion.



the units that stay in and those that drop-out from the study between t and $t+1$ may be noticed. The latter (individuals) present CD4 levels which are lower when compared to units remaining in the study beyond $t+1$, especially at the beginning of the observation window. These findings suggest the potential presence of some form of sample selection occurring as time goes by. To analyse the effect of observed covariates on the HIV progression and account for the missing data process, we have estimated a linear quantile hidden Markov model with LDO-dependent transitions. To give some insight into the sensitivity of

parameter estimates to modelling assumptions, we compare these results with those obtained from the corresponding MAR version, the lqHMM proposed by Farcomeni (2012). Being more severe HIV-related symptoms the main target of inference, we have decided to focus on lower CD4 count levels, that is on $\tau = (0.25, 0.50)$. For a generic quantile $\tau \in (0, 1)$, the following conditional model has been fit:

$$\mu_{it}(s_{it}) = \alpha(s_{it}) + \mathbf{x}'_{it}\boldsymbol{\beta}$$

where $\alpha(s_{it})$ denotes a state-dependent random intercept, and $\mathbf{x}_{it}$ includes two continuous covariates (years since seroconversion and age), the dummy variable drug (baseline: no) and three discrete variables (packs of cigarette per day, number of sexual partners and CESD score). Both lqHMM and lqHMM+QLDO have been fit for a varying number of hidden states ($m = 2, ..., 5$) and, if the case, for a varying number of LDO classes ($G = 2, ..., 5$). To reduce the chance of being trapped in local maxima, we have adopted the following multi-start strategy. For the hidden Markov chain, a first deterministic starting solution has been obtained by setting prior and transition probabilities to $\delta_h = 1/m$ and $q_{kh} = (1 + s\mathbb{I}(h = k))/(m + s), h, k = 1, ..., m$, (for a suitable constant s) for all the LDO classes (if present). Parameters in the missing data model have been initialized by fitting an ordered logit to the response obtained by discretizing the distribution of the number of visits for each individual. To avoid singularities, a fraction ξ of responses has been randomly perturbed. Initial values for the fixed longitudinal model parameters correspond to the maximum likelihood estimates of the linear quantile regression model under independence, while the time-varying random intercept has been initialized by adding Gaussian quadrature locations to the corresponding fixed intercept. Random starting values have been obtained by perturbing the deterministic ones. For each model (ie for each combination $[m, G]$), we have considered 30 starting points and retained the solution with the highest likelihood. In table 2, we report the corresponding AIC and the BIC values for such solutions. **As it was expected, because of the high number of parameters in the lqHMM+QLDO formulation, both criteria suggest to retain the solution with $m = 5$ and $G = 1$ for the quantiles we have considered. However, by looking at the AIC values, we may notice only slight differences between the solution $[m = 5, G = 1]$ and $[m = 5, G = 2]$. This suggests that, despite the highly parametrized structure of the lqHMM+QLDO formulation, model fit (as measured by the maximized log-likelihood value) is improved when accounting for the missing data generation process. Furthermore, simulation results in**

Table 2: CD4 data. Model selection; penalized likelihood criteria for different value of m and G at different quantiles.

	LDO classes			
Hidden States	1	2	3	4
		$\tau = 0.25$		
		AIC		
2	3247.36	3215.99	3218.02	3231.74
3	2895.26	2876.79	2870.91	2890.06
4	2655.24	2642.60	2646.09	2656.89
5	2550.21	2550.92	2556.75	2589.15
		BIC		
2	3298.20	3278.56	3292.32	317.77
3	2969.56	2978.47	2999.97	3046.49
4	2760.83	2799.03	2853.36	2915.01
5	2694.91	2777.74	2865.71	2980.23
		$\tau = 0.50$		
		AIC		
2	2688.11	2664.24	2665.12	2672.56
3	2448.49	2432.94	2436.74	2450.87
4	2310.55	2305.78	2308.59	2337.79
5	2239.02	2242.75	2255.94	2282.33
		BIC		
2	2738.95	2726.81	2739.42	2758.59
3	2522.79	2534.62	2565.80	2607.30
4	2416.15	2462.22	2515.86	2595.90
5	2383.72	2469.57	2564.90	2673.41

section 6 show that the BIC leads, in most of the cases, to models with a lower (than the truth) number of LDO classes. Last, as discussed by Molemberghs et al (2015), for any MNAR model we can find a MAR model with exactly the same fit. Therefore, since usually MNAR models are more complex than the corresponding MAR ones, as it is the case here, we could not rely on model fit only. Rather, our aim is to study the sensitivity of parameter estimates when we move far from the MAR assumption. In this sense, lqHMM+QLDO is a necessary counterpart to lqHMM in the pres-

ence of (potentially) non-ignorable missingess. Based on these findings, we will consider the model $[m = 5, G = 2]$ as the potential competitor for the MAR version (the lqHMM).

Table 3 reports the estimated parameters for the longitudinal data model under the lqHMM and the lqHMM+QLDO specifications, with corresponding 95% confidence intervals (within brackets). These have been computed using a block non-parametric bootstrap, with $B = 1000$ resamples. As it can be

Table 3: CD4 data. Estimated parameters for the longitudinal data model at different quantiles.

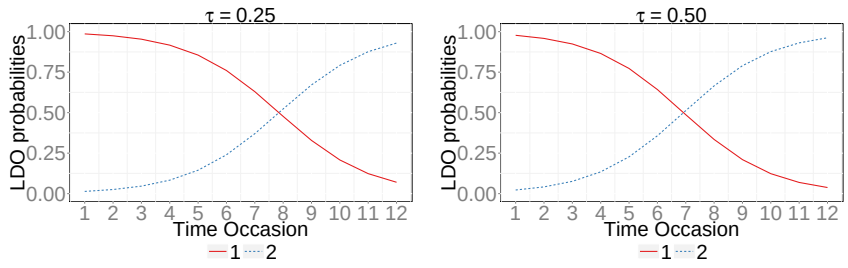
	lqHMM		lqHMM+QLDO	
		$\tau = 0.25$		
α_1	4.738	(3.238 ; 4.956)	4.728	(3.221 ; 4.944)
α_2	5.699	(5.395 ; 5.750)	5.693	(5.435 ; 5.752)
α_3	6.126	(6.051 ; 6.164)	6.118	(6.073 ; 6.155)
α_4	6.509	(6.413 ; 6.562)	6.500	(6.446 ; 6.549)
α_5	6.843	(6.757 ; 6.935)	6.832	(6.772 ; 6.922)
Age	0.001	(-0.006 ; 0.005)	0.001	(-0.006 ; 0.005)
Drugs	-0.033	(-0.084 ; 0.068)	-0.025	(-0.074 ; 0.062)
Packs	0.082	(0.051 ; 0.096)	0.082	(0.048 ; 0.095)
Partners	0.011	(0.002 ; 0.018)	0.010	(0.000 ; 0.017)
CESD	-0.004	(-0.006 ; -0.001)	-0.004	(-0.006 ; -0.001)
$\text{Time}_{\text{sero}}$	-0.091	(-0.121 ; -0.075)	-0.089	(-0.121 ; -0.073)
		$\tau = 0.50$		
α_1	5.628	(5.074 ; 5.753)	5.618	(5.142 ; 5.751)
α_2	6.198	(6.014 ; 6.252)	6.197	(6.060 ; 6.233)
α_3	6.524	(6.393 ; 6.574)	6.522	(6.450 ; 6.558)
α_4	6.805	(6.719 ; 6.874)	6.797	(6.753 ; 6.854)
α_5	7.191	(7.084 ; 7.291)	7.182	(7.112 ; 7.271)
Age	-0.003	(-0.007 ; 0.005)	-0.003	(-0.007 ; 0.005)
Drugs	0.036	(-0.016 ; 0.110)	0.038	(-0.007 ; 0.082)
Packs	0.049	(0.014 ; 0.068)	0.048	(0.011 ; 0.067)
Partners	0.002	(-0.003 ; 0.012)	0.001	(-0.004 ; 0.011)
CESD	-0.005	(-0.007 ; -0.001)	-0.005	(-0.007 ; -0.001)
$\text{Time}_{\text{sero}}$	-0.110	(-0.126 ; -0.084)	-0.108	(-0.125 ; -0.080)

easily noticed, age and drugs play no role in explaining the evolution of the CD4 cell counts over time. For both models, and for all the analysed quantiles, more severe depression symptoms lead to a decrease in the response variable; as expected, increases in the time since seroconversion corresponds to a reduction in the level of T-lymphocytes. The effect of $\text{Time}_{\text{sero}}$ is slightly reduced under the lqHMM with respect to the lqHMM+QLDO specification. Results for the remaining covariates follow. Smoking more cigarettes (for $\tau = 0.25$ and $\tau = 0.50$, with stronger effect in the former case) and having more sexual partners (for $\tau = 0.25$ only) are associated to higher CD4 cell counts. According to Zeger and Diggle (1994), the positive effect of such risk factors may be due to immune response stimulation or, simply, to a form of selection bias: healthier men stay longer in the study and continue their usual practices. Regarding state-dependent intercepts, the estimates increase with the quantile level and, in all the analysed models, higher CD4 cell counts correspond to "higher" hidden states. When comparing results obtained under the lqHMM and the lqHMM+QLDO specification, no substantial differences can be observed; this suggests that the class of models we are considering is rather robust with respect to possible misspecification of the missing data generating mechanism. However, when looking at the bootstrap confidence intervals, slight differences emerge. That is, if we consider the missing data process, we obtain narrower intervals and, therefore, parameter estimates turns out to be more reliable. By matching the results discussed so far with the estimated initial and transition probabilities, more thoughtful information on individual trajectories can be obtained. In table 8, we report the Markov chain parameters estimated under the lqHMM formulation. For $\tau = 0.25$, it is clear that most of the patients start the study with a medium/high level of CD4 cell counts ($\delta_3 + \delta_4 + \delta_5 > 0.9$). As the time passes by, the estimated $\mathbf{Q}$ matrix highlights a high variability in the longitudinal trajectories. Transitions between states are quite likely; units being in lower hidden states generally tend to move towards higher baseline values. When analysing results we have obtained for the median ($\tau = 0.50$), a different evolution of the response variable seems to be recovered. Here, intermediate hidden states are the most likely at the beginning of the observation window ($\delta_2 + \delta_3 + \delta_4 > 0.85$) and transitions between states are less frequent than those observed for $\tau = 0.25$ ($q_{hh} > 0.8, \forall h = 1, ..., m$). If any transition is observed, the probability of moving towards "lower" states is slightly higher than that of moving towards the highest ones.

The analysis of results obtained under the lqHMM+QLDO specification can help understanding the effect of a potentially non-ignorable missingess.

In figure 2, we report the estimated LDO class probabilities. It may be noticed that, for both quantiles, higher classes are associated with increasing time to drop-out. That is, units staying longer into the study belong to the second LDO class. We report in tables 9-10 the estimates for the initial and

Fig. 2: CD4 data. LDO class probabilities for $\tau = 0.25$ (left) and $\tau = 0.50$ (right).



the transition probabilities under the lqHMM+QLDO specification for the two classes (LDO_1 and LDO_2). Initial probability estimates, for all the analysed quantiles, suggest that the first hidden state is quite unlikely at the beginning of the study. Units are almost equally distributed over the remaining states. Concerning the transition probability matrices, parameter estimates highlight the presence of individuals in the sample who experience quite a different disease progression over time. Class LDO_1 is characterized by shorter individual sequences and mostly include subjects who leave the study in the first few occasions. Within this class, the estimated transitions for $\tau = 0.25$ are quite similar to those observed for the lqHMM specification. Units with a particularly low CD4 count move towards "higher" hidden states. The only remarkable difference between lqHMM and lqHMM+QLDO is related to $\hat{q}_{11}$ that, under the latter approach, is much higher ($\hat{q}_{11}(\text{LDO}_1) = 0.931$ vs $\hat{q}_{11} = 0.798$). This is probably due to some units in the sample that leave the study with very low CD4 levels and that, under the MAR approach, are not clearly identified. When we look at the results for $\tau = 0.50$, the estimated transitions suggest a progressive reduction in the median response over time. Comparing results obtained under the MNAR and the MAR approach, it is clear that such an evolution is better identified when accounting for the missing data process. In fact, under the LDO specification, the probability of moving towards the "lowest" state is higher than that observed for lqHMM and with probability equal to one individuals do not further move. This result helps detect units

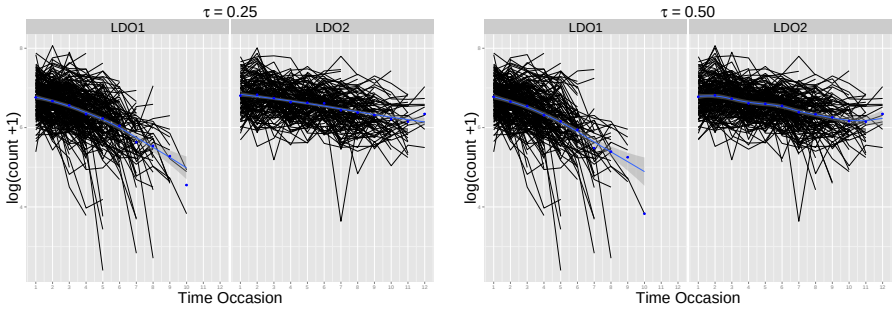
that drop-out early from the study after experiencing a steep and sudden reduction in CD4 count levels.

Focusing on class LDO_2 (ie the class associated with units staying longer into the study) different longitudinal paths can be observed. When considering the left tail of the response distribution ($\tau = 0.25$), the first two hidden states are seldom visited and, if any transition is observed, units move towards "higher" states in at the next occasion. The only exception is for the estimate $\hat{q}_{31} = 0.184$ which is probably associated to some units that experience a sudden decrease in the CD4 level followed by an increase at the subsequent visit. Regarding the other hidden states, if any transition is observed, units generally tend to move towards higher baseline values. A similar path can be observed for the median response, $\tau = 0.50$, where the estimated $\mathbf{Q}$ matrix is almost diagonal, apart from the first hidden state which is, however, seldom reached. Also in this case, as for $\tau = 0.25$, if any transition is observed, this is generally towards higher intercept values.
To support the results we have discussed so far, we report in figure 3 the longitudinal trajectories of individuals classified (via a MAP criterion) into LDO_1 (left) and LDO_2 (right), for $\tau = 0.25$ and $\tau = 0.50$. Local polynomial regression curves (blue lines), 95% confidence intervals (gray bands) and mean values (blue dots) are reported. Due to the missing data process, wider confidence intervals are observed at the last measurement occasions. As expected, units in LDO_1 class leave the study earlier in time and experience a more evident reduction in the CD4 counts during the follow-up time. On the other hand, longer longitudinal sequences and more stable response patterns are observed for those units who are classified in LDO_2, both for $\tau = 0.25$ and $\tau = 0.50$. While we can not postulate the proposed model is correct and the lqHMM is not (this is not our aim indeed), we may observe that, by considering an inhomogeneous hidden Markov representation due to a non random missing data generating process, some of the parameter estimates slightly change interpretation and we get a more complete and coherent picture of the response variable dynamics.

6 Simulation study

To evaluate the empirical behaviour of the proposed model, we have performed the following simulation study. Data have been generated from a Gausian HMM+QLDO with $m = 4$ states and $G = 2$ LDO classes. For the missing data model, we have considered the following set of model parameters: $\boldsymbol{\lambda} =$

Fig. 3: CD4 data. Longitudinal trajectories by LDO class, for $\tau = 0.25$ (left) and $\tau = 0.50$ (right).



$(4.41, -0.63)$. Based on such values, "higher" LDO classes are associated to longer longitudinal sequences. Initial probabilities for the hidden Markov chain have been fixed to $\boldsymbol{\delta} = (0.05, 0.39, 0.48, 0.08)$, while transition probabilities have been set equal to

$$\mathbf{Q}(\text{LDO}_1) = \begin{pmatrix} 1.00 & 0.00 & 0.00 & 0.00 \\ 0.27 & 0.73 & 0.00 & 0.00 \\ 0.00 & 0.23 & 0.71 & 0.06 \\ 0.05 & 0.06 & 0.00 & 0.89 \end{pmatrix} \quad \mathbf{Q}(\text{LDO}_2) = \begin{pmatrix} 0.91 & 0.09 & 0.00 & 0.00 \\ 0.05 & 0.92 & 0.03 & 0.00 \\ 0.02 & 0.03 & 0.94 & 0.01 \\ 0.00 & 0.00 & 0.01 & 0.99 \end{pmatrix}$$

Based on these parameter values, individuals belonging to the first LDO class move towards "lower" hidden states with a higher probability than units belonging to the second class. We have decided to reduce the distance between the transition probability matrices associated to the LDO classes when compared to those estimated on the real data. This has been done to verify the ability of the estimation algorithm in recovering the "true" latent structure. As regards the longitudinal observations, covariates available for the CD4 dataset have been directly considered. The following values for the fixed parameters have been fixed: $\beta_{\text{timeSero}} = -0.088, \beta_{\text{age}} = 0.006, \beta_{\text{drugs}} = 0.148, \beta_{\text{packs}} = 0.055, \beta_{\text{partners}} = 0.009, \beta_{\text{cesd}} = -0.004$; on the other hand, state-specific random intercepts have been set to $\alpha = \{5.861, 6.306, 6.650, 7.039\}$.

Based on these parameters, we have simulated the response variable from a Gaussian distribution, with variance $\sigma^2 = 0.23$, corresponding to the variance for the AL density estimated in the real data application at $\tau = 0.50$. Mean

values have been defined according to the following model

$$\mu_{it}(s_{it}) = \alpha(s_{it}) + \mathbf{x}'_{it}\boldsymbol{\beta},$$

We have simulated $B = 200$ samples and estimated a lqHMM+QLDO for different quantiles, $\tau = \{0.25, 0.50\}$, and for different choices of m and G, $m = \{3, 4, 5\}$ and $G = \{1, 2, 3\}$.

The bias and the standard deviation of parameter estimates for the longitudinal data model, for fixed $m = 4$ and $G = 2$, are reported in table 4. As it

Table 4: Simulation study. Bias and standard deviation of longitudinal model parameters for the lqHMM+QLDO with $m = 4$ and $G = 2$. $\tau = \{0.25, 0.50\}$. $B = 200$ simulated samples

	$\tau = 0.25$		$\tau = 0.50$	
	Bias	Sd	Bias	Sd
α_1	0.0099	0.0027	0.0102	0.0013
α_2	0.0150	0.0008	0.0134	0.0034
α_3	0.0222	0.0018	0.0109	0.0018
α_4	0.0230	0.0204	0.0050	0.0075
β_{timeSero}	-0.0017	0.0026	0.0011	0.0009
β_{age}	-0.0004	0.0004	-0.0002	0.0001
β_{drugs}	-0.0073	0.0027	-0.0118	0.0031
β_{packs}	0.0005	0.0010	0.0002	0.0012
β_{partners}	-0.0006	0.0007	0.0001	0.0003
β_{cesd}	0.0000	0.0001	0.0000	0.0001

is expected, a higher bias is observed for the parameters related to the hidden Markov chain when compared to the fixed effect estimates. The quality of results reduces (that is the bias and the sd tend to increase) when considering the left tail of the response distribution since it represents a low density region with reduced information.

We report in tables 5-6 the bias and the standard deviation (within brackets) of the estimated transition probability matrices for the LDO classes considering $\tau = 0.25$ and $\tau = 0.50$, respectively. For both quantiles, parameters are estimated with good accuracy in term of bias and (relatively) low variability, whatever the LDO class and the hidden state.

Table 5: Simulation study. Bias and standard deviation (within brackets) of transition probability matrices for the lqHMM+QLDO with $m = 4$ and $G = 2$. $\tau = 0.25$. $B = 200$ simulated samples

	1	2	3	4
$\texttt{LDO}_1$				
1	-0.002 (0.00)	0.002 (0.00)	0.000 (0.00)	0.000 (0.00)
2	-0.041 (0.01)	0.041 (0.01)	0.000 (0.00)	0.000 (0.00)
3	0.000 (0.00)	-0.074 (0.03)	0.062 (0.06)	0.011 (0.03)
4	0.002 (0.02)	-0.032 (0.02)	0.000 (0.00)	0.030 (0.03)
$\texttt{LDO}_2$				
1	0.017 (0.00)	-0.017 (0.00)	0.000 (0.00)	0.000 (0.00)
2	0.012 (0.02)	-0.009 (0.02)	-0.003 (0.00)	0.000 (0.00)
3	0.007 (0.01)	-0.006 (0.01)	0.004 (0.01)	-0.005 (0.00)
4	0.005 (0.00)	0.024 (0.01)	-0.004 (0.00)	-0.025 (0.02)

Table 6: Simulation study.Bias and standard deviation (within brackets) of transition probability matrices for the lqHMM+QLDO with $m = 4$ and $G = 2$. $\tau = 0.50$. $B = 200$ simulated samples

	1	2	3	4
$\texttt{LDO}_1$				
1	-0.003 (0.00)	0.003 (0.00)	0.000 (0.00)	0.000 (0.00)
2	-0.042 (0.02)	0.042 (0.02)	0.000 (0.00)	0.000 (0.00)
3	0.007 (0.00)	-0.054 (0.02)	0.032 (0.03)	0.014 (0.01)
4	-0.004 (0.01)	-0.034 (0.01)	0.000 (0.00)	0.038 (0.03)
$\texttt{LDO}_2$				
1	0.027 (0.01)	-0.027 (0.01)	0.000 (0.00)	0.000 (0.00)
2	0.015 (0.01)	-0.008 (0.01)	-0.007 (0.00)	0.000 (0.00)
3	0.004 (0.00)	-0.002 (0.01)	-0.001 (0.01)	-0.001 (0.00)
4	0.007 (0.00)	0.026 (0.01)	-0.004 (0.00)	-0.029 (0.01)

Last, in table 7, we show the distribution of the estimated number of hidden states and LDO classes, using the AIC and the BIC criteria. As it is clear, AIC outperforms BIC in recovering the true number of states and classes. In fact, BIC tends to heavily penalize highly parametrized models. In the present context, for both quantiles, the BIC index suggests to adopt a lqHMM, that

Table 7: Simulation study. Performance of penalized likelihood critera. Values of m and G estimated with BIC and AIC. $\tau = \{0.25, 0.50\}$. $B = 200$ simulated samples

	BIC			AIC		
	$G = 1$	$G = 2$	$G = 3$	$G = 1$	$G = 2$	$G = 3$
			$\tau = 0.25$			
$m = 3$	0.00	0.00	0.00	0.00	0.00	0.00
$m = 4$	0.99	0.01	0.00	0.00	1.00	0.00
$m = 5$	0.00	0.00	0.00	0.00	0.00	0.00
			$\tau = 0.50$			
$m = 3$	0.00	0.00	0.00	0.00	0.00	0.00
$m = 4$	0.97	0.03	0.00	0.00	0.89	0.00
$m = 5$	0.00	0.00	0.00	0.00	0.11	0.00

is a lqHMM+QLDO with a single LDO class (ie $G = 1$). On the contrary, AIC seems to recover with higher accuracy the real model structure and it should be considered as a better choice to estimate m and G. When comparing $\tau = 0.25$ and $\tau = 0.50$, slightly better results are obtained in the former case. AIC always identifies the right model for $\tau = 0.25$, while some anomalies can be observed for $\tau = 0.50$, where, in 11% of samples, a further hidden state is selected. This is probably due to a more variable behaviour in terms of state-specific locations which can be seldom observed at $\tau = 0.25$.

To summarize, results we have obtained highlight the effectiveness of the estimation algorithm in recovering the "true", underlying, model structure. The quality of parameter estimates we have obtained in this simulation study suggests that the results presented in section 5 for the CD4 data analysis may be considered as quite reliable. The proposed model can be seen as a valid and flexible approach to handle informative missing data patterns while controlling for time-varying sources of unobserved heterogeneity in longitudinal profiles. While the choice of letting $\mathbf{Q}$ vary with the LDO class may lead to a substantial increase in the number of parameters, it may help describe the changes in the behaviour of units with a (possibly) different propensity to drop-out from the study.

7 Conclusions

Quantile regression represents an interesting alternative to standard mean regression when the researcher's interest is on the tails of the response variable distribution and/or potential outliers may affect the mean values. When responses are repeatedly measured over time on the same sample units, dependence between observations has to be taken into consideration to ensure valid inferential conclusions. In the presence of a potentially informative missing data mechanism, however, parameter estimates may result biased due to the "selection" of units remaining under observation. In this paper, we propose a linear quantile hidden Markov model with drop-out dependent transitions. Within this framework, we obtain a more detailed picture of the response variable distribution and, jointly, address the problem of potentially non-ignorable missingness. More in detail, the latent drop-out class variable allows to capture (time-invariant) unobserved sources of heterogeneity shared by individuals with a similar propensity to drop-out. Such propensities lead to different transitions across the states of the hidden Markov chain; the marginal model for the longitudinal response is, therefore, given by a finite mixture of lqHMMs.

We have re-analysed a benchmark dataset and compared the results with those obtained under the "standard" lqHMM by Farcomeni (2012). Although with the proposed approach the number of parameters consistently increases, a clearer description of the observed data is obtained; this renders the proposed methodology an interesting and valuable alternative to existing modelling approaches.

Table 8: CD4 data. Estimated initial and transition probabilities at different quantiles for the lqHMM, $m = 5$.

	1		2		3		4		5	
$\tau = 0.25$										
δ	0.002	(0.000 ; 0.009)	0.033	(0.000 ; 0.070)	0.333	(0.231 ; 0.431)	0.426	(0.342 ; 0.529)	0.206	(0.100 ; 0.300)
1	0.798	(0.374 ; 1.000)	0.040	(0.000 ; 0.273)	0.129	(0.000 ; 0.501)	0.000	(0.000 ; 0.464)	0.033	(0.000 ; 0.184)
2	0.137	(0.067 ; 0.208)	0.660	(0.436 ; 0.778)	0.203	(0.090 ; 0.429)	0.000	(0.000 ; 0.029)	0.000	(0.000 ; 0.020)
3	0.004	(0.000 ; 0.028)	0.137	(0.080 ; 0.195)	0.689	(0.568 ; 0.787)	0.155	(0.093 ; 0.250)	0.015	(0.000 ; 0.046)
4	0.009	(0.000 ; 0.017)	0.035	(0.000 ; 0.070)	0.158	(0.100 ; 0.232)	0.744	(0.656 ; 0.808)	0.055	(0.021 ; 0.109)
5	0.000	(0.000 ; 0.005)	0.008	(0.000 ; 0.026)	0.045	(0.002 ; 0.087)	0.050	(0.000 ; 0.109)	0.896	(0.839 ; 0.955)
$\tau = 0.50$										
δ	0.000	(0.000 ; 0.000)	0.219	(0.060 ; 0.310)	0.360	(0.238 ; 0.499)	0.326	(0.202 ; 0.441)	0.095	(0.042 ; 0.149)
1	0.933	(0.802 ; 1.000)	0.067	(0.000 ; 0.198)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)
2	0.068	(0.031 ; 0.126)	0.847	(0.742 ; 0.920)	0.085	(0.004 ; 0.179)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)
3	0.026	(0.000 ; 0.066)	0.086	(0.030 ; 0.163)	0.827	(0.718 ; 0.902)	0.061	(0.002 ; 0.135)	0.000	(0.000 ; 0.002)
4	0.002	(0.000 ; 0.018)	0.065	(0.011 ; 0.106)	0.032	(0.000 ; 0.105)	0.861	(0.805 ; 0.910)	0.040	(0.012 ; 0.072)
5	0.003	(0.000 ; 0.017)	0.027	(0.000 ; 0.070)	0.000	(0.000 ; 0.045)	0.043	(0.000 ; 0.115)	0.927	(0.857 ; 0.983)

Table 9: CD4 data- Estimated initial and transition probabilities for the lqHMM+QLDO, $m = 5$, $G = 2$ and LDO_1.

	1		2		3		4		5	
$\tau = 0.25$										
δ	0.006	(0.000 ; 0.019)	0.197	(0.153 ; 0.232)	0.259	(0.228 ; 0.292)	0.269	(0.243 ; 0.300)	0.269	(0.224 ; 0.322)
1	0.931	(0.715 ; 1.000)	0.069	(0.000 ; 0.241)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.102)
2	0.088	(0.049 ; 0.132)	0.663	(0.525 ; 0.767)	0.239	(0.124 ; 0.384)	0.011	(0.000 ; 0.053)	0.000	(0.000 ; 0.000)
3	0.015	(0.000 ; 0.039)	0.144	(0.089 ; 0.229)	0.704	(0.546 ; 0.782)	0.137	(0.072 ; 0.260)	0.000	(0.000 ; 0.016)
4	0.000	(0.000 ; 0.020)	0.080	(0.011 ; 0.153)	0.087	(0.011 ; 0.250)	0.772	(0.576 ; 0.860)	0.062	(0.001 ; 0.151)
5	0.005	(0.000 0.015)	0.021	(0.000 ; 0.089)	0.123	(0.004 ; 0.213)	0.042	(0.000 ; 0.159)	0.809	(0.681 ; 0.907)
$\tau = 0.50$										
δ	0.000	(0.000 ; 0.004)	0.200	(0.073 ; 0.299)	0.332	(0.200 ; 0.479)	0.363	(0.229 ; 0.449)	0.104	(0.062 ; 0.153)
1	1.000	(0.917 ; 1.000)	0.000	(0.000 ; 0.083)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)
2	0.138	(0.056 ; 0.222)	0.793	(0.661 ; 0.898)	0.069	(0.000 ; 0.215)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.018)
3	0.036	(0.000 ; 0.118)	0.240	(0.088 ; 0.404)	0.724	(0.183 ; 0.846)	0.000	(0.000 ; 0.461)	0.000	(0.000 ; 0.000)
4	0.000	(0.000 ; 0.022)	0.116	(0.001 ; 0.275)	0.123	(0.000 ; 0.302)	0.721	(0.551 ; 0.826)	0.040	(0.000 ; 0.114)
5	0.010	(0.000 ; 0.039)	0.107	(0.000 ; 0.223)	0.057	(0.000 ; 0.277)	0.000	(0.000 ; 0.364)	0.826	(0.527 ; 0.955)

Table 10: CD4 data. Estimated initial and transition probabilities for the lqHMM+QLDO, $m = 5$, $G = 2$ and LDO_2.

	1		2		3		4			
$\tau = 0.25$										
δ	0.006	(0.000 ; 0.019)	0.197	(0.153 ; 0.232)	0.259	(0.228 ; 0.292)	0.269	(0.243 ; 0.300)	0.269	(0.224 ; 0.322)
1	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)	1.000	(1.000 ; 1.000)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)
2	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.160)	0.000	(0.000 ; 0.047)	0.726	(0.000 ; 1.000)	0.274	(0.000 ; 1.000)
3	0.184	(0.000 ; 0.994)	0.000	(0.000 ; 0.000)	0.816	(0.000 ; 1.000)	0.000	(0.000 ; 0.124)	0.000	(0.000 ; 0.000)
4	0.007	(0.000 ; 0.052)	0.064	(0.000 ; 0.177)	0.046	(0.000 ; 0.197)	0.763	(0.035 ; 0.906)	0.121	(0.003 ; 0.754)
5	0.000	(0.000 0.000)	0.006	(0.000 ; 0.168)	0.000	(0.000 ; 0.024)	0.005	(0.000 ; 0.150)	0.989	(0.765 ; 1.000)
$\tau = 0.50$										
δ	0.000	(0.000 ; 0.004)	0.200	(0.073 ; 0.299)	0.332	(0.200 ; 0.479)	0.363	(0.229 ; 0.449)	0.104	(0.062 ; 0.153)
1	0.515	(0.000 ; 1.000)	0.485	(0.079 ; 1.000)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)	0.000	(0.000 ; 0.000)
2	0.000	(0.000 ; 0.062)	0.919	(0.438 ; 1.000)	0.081	(0.000 ; 0.721)	0.000	(0.000 ; 0.032)	0.000	(0.000 ; 0.000)
3	0.018	(0.000 ; 0.058)	0.011	(0.000 ; 0.111)	0.900	(0.763 ; 0.975)	0.071	(0.003 ; 0.248)	0.000	(0.000 ; 0.000)
4	0.000	(0.000 ; 0.020)	0.020	(0.000 ; 0.055)	0.021	(0.000 ; 0.089)	0.919	(0.862 ; 0.968)	0.040	(0.000 ; 0.087)
5	0.000	(0.000 ; 0.021)	0.000	(0.000 ; 0.028)	0.000	(0.000 ; 0.000)	0.039	(0.000 ; 0.130)	0.961	(0.889 ; 1.000)

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