
A study on serum calcium and phosphate in dialysis patients via a mixed effects latent Markov model with two outcomes

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Categorical Longitudinal Data

- Repeated measures of a categorical outcome for many subjects, over time
- Classical situation: one binary outcome.
- Classical modeling approach: logistic model with random effects

Formally,

$$\log \frac{P(Y_{it} = 1 | \mathbf{X}_{it})}{P(Y_{it} = 0 | \mathbf{X}_{it})} = \alpha_i + \boldsymbol{\beta}' \mathbf{X}_{it},$$

where $\alpha_i \sim N(0, \sigma^2)$ (see Pendergast *et al.*, 1996);
 $i = 1, \dots, n, t = 1, \dots, T_i$.

Motivating example

Recently issued K/DOQI ranges recommend the following levels for serum calcium and phosphate:

$$8.5\text{mg/dl} \leq Ca \leq 9.5\text{mg/dl}$$

$$3.5\text{mg/dl} \leq P \leq 5.5\text{mg/dl}$$

Dialysis patients are classified as *non-respondent* when having high levels of Calcium, Phosphate, or parathyroid hormone.

Non-respondent patients often undergo parathyroidectomy.

The research question was: *Is surgery effective in targeting the K/DOQI ranges?*

Motivating example: Data

Data were collected on patients receiving surgery at our hospital and firstly analyzed by Mazzaferro *et al.* (2008).

- Dataset concerning $n = 77$ subjects with a maximum of five follow-up times (baseline; 1m,1y,3y,5y after surgery)
- Two binary response variables:
 - ▷ *Calcium*: equal to 1 if within K-DOQI ranges
 - ▷ *Phosphate*: equal to 1 if within K-DOQI ranges

Limits of the classical approach

- We need to model the two outcomes simultaneously
- Two assumptions on random effects which we want to drop:
 - ▷ the normality assumption
 - ▷ the assumption that they are time-fixed: $\alpha_i \rightarrow \alpha_{it}$ (see Hsiao, 2005).

Proposed model

The model we propose is based on two marginal logits and one log-odds ratio:

$$\log \frac{p(y_{1it} = 1 | \mathbf{x}_{it}, \mathbf{y}_{i,t-1})}{p(y_{1it} = 0 | \mathbf{x}_{it}, \mathbf{y}_{i,t-1})} = \alpha_{1it} + \mathbf{x}'_{it} \boldsymbol{\beta}_1 + \mathbf{y}'_{i,t-1} \boldsymbol{\gamma}_1$$

$$\log \frac{p(y_{2it} = 1 | \mathbf{x}_{it}, \mathbf{y}_{i,t-1})}{p(y_{2it} = 0 | \mathbf{x}_{it}, \mathbf{y}_{i,t-1})} = \alpha_{2it} + \mathbf{x}'_{it} \boldsymbol{\beta}_2 + \mathbf{y}'_{i,t-1} \boldsymbol{\gamma}_2$$

$$\begin{aligned} & \log \frac{p(y_{1it} = 1, y_{2it} = 1 | \mathbf{x}_{it}, \mathbf{y}_{i,t-1})}{p(y_{1it} = 1, y_{2it} = 0 | \mathbf{x}_{it}, \mathbf{y}_{i,t-1})} + \\ & + \log \frac{p(y_{1it} = 0, y_{2it} = 0 | \mathbf{x}_{it}, \mathbf{y}_{i,t-1})}{p(y_{1it} = 0, y_{2it} = 1 | \mathbf{x}_{it}, \mathbf{y}_{i,t-1})} = \phi \end{aligned}$$

Comments

- Not necessarily the same covariates used on each marginal logit
- γ_h estimates the adjusted effect of $\mathbf{Y}_{i,t-1}$ on the current outcome. This is known as *state dependence*.
- This model is a special case of the class of models proposed in Bartolucci and Farcomeni (2009), who show how to model any combination of any number of categorical outcomes

Random Intercepts

For each i and t , the random parameter vector α_{it} is assumed to come from a *discrete* distribution with k support points.

The k support points are denoted by ξ_c , $c = 1, \dots, k$.

We then need only model $P(\alpha_{it} = \xi_c)$, $c = 1, \dots, k$; and the fact that it evolves over time (i.e., dependence of α_{it} over α_{iv} , $v < t$.)

Latent Markov chain

For each i , the random parameter vectors $\{\alpha_{i1}, \dots, \alpha_{iT}\}$ are assumed to follow a (unobservable) *first-order Markov chain* with

- initial probabilities $P(\alpha_{i1} = \xi_c) = \lambda_c(\mathbf{y}_{i0}, \mathbf{x}_{i0})$, $c = 1, \dots, k$
- transition probabilities $P(\alpha_{it} = \xi_c | \alpha_{i,t-1} = \xi_d) = \pi_{cd}$;
 $c, d = 1, \dots, k$

It can be shown that modeling the initial probabilities as a function of $(\mathbf{y}_{i0}, \mathbf{x}_{i0})$ adjusts the regression parameters for *selection bias*.

Latent Markov vs Normal random effects

- It is not easy to check the normality assumption.
- Any latent distribution (including the normal) can be arbitrarily well approximated with k point masses.
- When the latent variable is truly normal, there is a mild loss of efficiency. When it is not, there is a substantial bias reduction.

Model Fit

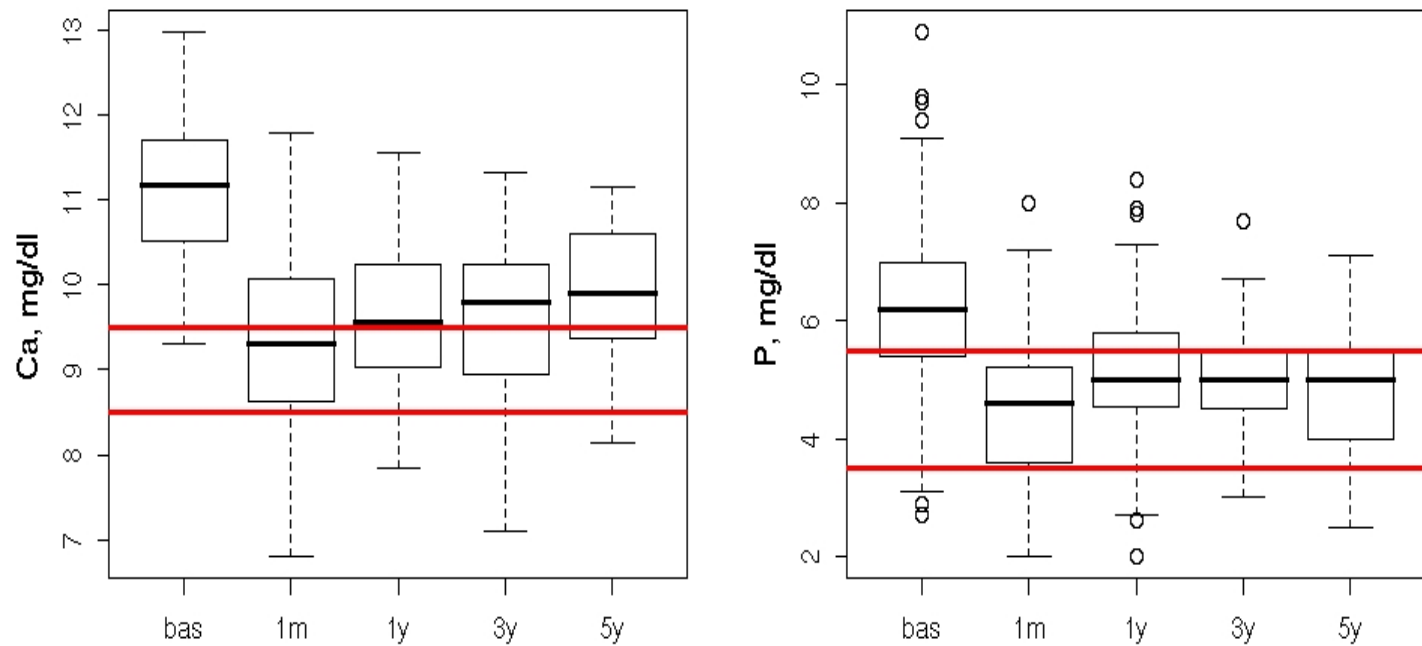
We give no details here on model fitting.

Refer to Bartolucci and Farcomeni (2009) for a description of an EM strategy for deriving the maximum likelihood estimates for the model.

At the E-step, we make use of forward and backward recursions adapted from the hidden Markov literature.

At the M-step, we set up ad-hoc Fisher-scoring iterations.

Calcium and Phosphate data: A graphical illustration



Estimates for $k = 2$

We used Akaike Information Criterion (AIC) to choose $k = 2$.
An asterisk indicates significance at 5% level.

$\text{logit}(\lambda_c(\mathbf{y}_{i0}, \mathbf{x}_{i0})) = \alpha_c + \beta' \text{baseline levels}.$

Effect	Calcium	Phosphate	log-odds
intercept	α_{1it}	α_{2it}	-0.055
$t = 1y$	-0.97	-1.06	-
$t = 3y$	-0.63	-1.75*	-
$t = 5y$	-1.08	-2.13*	-
age/100	0.01	-0.41	-
sex(M)	-0.52	-0.31	-
lagged calcium	1.20*	0.59*	-
lagged phosphate	0.23	1.00*	-

Was it worth the modeling? Biased restrictions:

Do we really need a model with time-varying non-normal latent Markov random effects which simultaneously handled the two outcomes?

- Two separate models (lose about 14% of predictive ability)
- Time-constant random effects (the model is rejected with $p < 0.001$)
- Normal random effects (the model is rejected with $p < 0.001$)

Further, simultaneous modeling leads us to unveil important information which was not noted by Mazzaferro *et al.* (2008), like the state dependence of calcium on phosphate.