Slide 1

Multilevel modelling of ordered and unordered categorical responses

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Slide 2

Outline

- Ordered categorical responses
  - Single-level models
  - Multilevel models
    - Two-level random intercept models
    - Cluster-specific and population average effects
    - Multilevel random coefficient models
  - Estimation methods
  - Analysis of cluster randomized trial of sex education
- Unordered categorical responses
  - Single-level models
  - Multilevel models
  - Analysis of abuse of antibiotics in young children in China

Slide 3

I. Ordered categorical responses

- Only a small number of responses or 'categories' are possible, y_s, $s = 1, \cdots, S$
- The categories are ordered,

$$y_1 < y_2 < \cdots < y_S, \quad \text{we'll set } y_s = s$$

- Examples:
  - Severity of symptoms (e.g. pain): 'none', 'moderate', 'severe'
  - Frequency of symptoms: 'never', 'occasionally', 'nearly every day', 'every day'
  - Response to treatment: 'progressive disease', 'no change', 'partial remission', 'complete remission'
  - Diagnosis: 'non-autistic', 'PDD-NOS' (pervasive development disorder), 'autistic'
  - Test results (e.g. breathing): 'normal', 'borderline', 'abnormal'
  - Satisfaction with treatment: 'very dissatisfied', 'dissatisfied', 'satisfied', 'very satisfied'

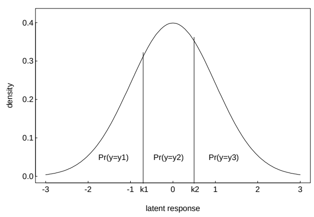
Slide 4

Latent response models

- Underlying the observed ordinal response y_i for subject i is a latent (unobserved) continous response y_i^*.
- A threshold model determines the observed response:

$$y_i = \begin{cases} 1 & \text{if} \quad y_i^* \le \kappa_1 \\ 2 & \text{if} \quad \kappa_1 < y_i^* \le \kappa_2 \\ \vdots & \vdots \quad \vdots \\ S & \text{if} \quad \kappa_{S-1} < y_i^*, \end{cases}$$

- For a probit model, $y_i^* \sim N(0,1)$, with $S = 3$ categories:



- The latent response is modelled as a linear regression without an intercept (for identification)

$$\begin{aligned} y_i^* &= \beta_1 x_{1i} + \beta_2 x_{2i} + \cdots + \epsilon_i \\ &= \boldsymbol{\beta}' \mathbf{x}_i + \epsilon_i \end{aligned}$$

Slide 5

Generalized linear models

- The cumulative probabilities are modeled as

$$\Pr(y_i > s) = F(\boldsymbol{\beta}'\mathbf{x}_i - \kappa_s),\ \ s = 1, \cdots, S-1,$$

giving *cumulative* models. F is the inverse *link function*

- Proportional odds model (logit link):

$$\Pr(y_i > s) = \frac{\exp(\boldsymbol{\beta}'\mathbf{x}_i - \kappa_s)}{1 + \exp(\boldsymbol{\beta}'\mathbf{x}_i - \kappa_s)}$$

$$\log\left[\frac{\Pr(y_i > s)}{1 - \Pr(y_i > s)}\right] = \boldsymbol{\beta}'\mathbf{x}_i - \kappa_s$$

  – The exponentiated regression coefficients can be interpreted as odds ratios for high versus low scores regardless of cut-point (proportional odds):

$$\frac{\Pr(y_i > s)/[1 - \Pr(y_i > s)]}{\Pr(y_j > s)/[1 - \Pr(y_j > s)]} = \exp(\boldsymbol{\beta}'\{\mathbf{x}_i - \mathbf{x}_j\})$$

- Cumulative models are equivalent to latent response models:

Model	Link F^{-1}	Distribution of ϵ_i	Variance of ϵ_i
Proportional odds	logit	logistic	$\pi^2/3$
Ordinal probit	probit	standard normal	1
Compl. log-log	Compl. log-log	Gumbel	$\pi^2/6$

Slide 6

Two-level random intercept models

- Subjects i nested in clusters j (e.g. hospitals). Include a random intercept u_j for clusters in the latent response model

$$y^*_{ij} = \boldsymbol{\beta}'\mathbf{x}_{ij} + u_j + \epsilon_{ij},\ \ u_j \sim N(0, \tau^2),\ \ u_j \text{ indep. of } \epsilon_{ij}.$$

- The total residual $\xi_{ij} = u_j + \epsilon_{ij}$ has variance

$$\text{var}(\xi_{ij}) = \begin{cases} \tau^2 + 1 & \text{for probit models} \\ \tau^2 + \pi^2/3 & \text{for logit models} \end{cases}$$

- The covariance between the total residuals ξ_{ij} and $\xi_{i'j}$ of two subjects in the same cluster is τ^2 and the *intraclass correlation* is

$$\rho \equiv \text{Cor}(\xi_{ij}, \xi_{i'j}) = \begin{cases} \tau^2/(\tau^2 + 1) & \text{for probit models} \\ \tau^2/(\tau^2 + \pi^2/3) & \text{for logit models} \end{cases}$$

- The latent responses for two units in the same cluster are conditionally independent given the random intercept:

$$\text{Cor}(y^*_{ij}, y^*_{i'j}|\mathbf{x}_{ij}, u_j) = 0$$

If we do not condition on the random intercept, the correlation is the intraclass correlation

$$\text{Cor}(y^*_{ij}, y^*_{i'j}|\mathbf{x}_{ij}) = \rho$$

Slide 7

Cluster-specific versus population average effects

- For a probit model, the 'marginal' or population average response probabilities are

$$\begin{aligned}\Pr(y_{ij} > s) &= \Pr(y_i^* > \kappa_s) = \Pr(\boldsymbol{\beta}'\mathbf{x}_{ij} + \xi_{ij} > \kappa_s)\\ &= \Pr(-\xi_{ij} \leq \boldsymbol{\beta}'\mathbf{x}_{ij} - \kappa_s)\\ &= \Pr\left(\frac{\xi_{ij}}{\sqrt{\tau^2+1}} \leq \frac{\boldsymbol{\beta}'\mathbf{x}_{ij} - \kappa_s}{\sqrt{\tau^2+1}}\right)\\ &= \Phi\left(\frac{\boldsymbol{\beta}'\mathbf{x}_{ij} - \kappa_s}{\sqrt{\tau^2+1}}\right),\end{aligned}$$

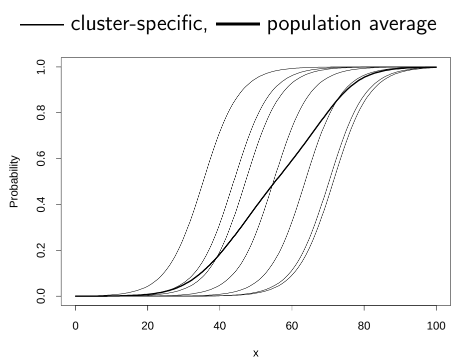
  where $\xi_{ij} = u_j + \epsilon_{ij}$.
  - Therefore, the marginal effects of $\mathbf{x}_{ij}$ are $\boldsymbol{\beta}/\sqrt{\tau^2+1}$. To achieve a given marginal effect, $\boldsymbol{\beta}$ must increase if τ^2 increases.
- The 'conditional' probabilities for a given cluster j are

$$\Pr(y_{ij} > s|u_j) = \Phi\left(\frac{\boldsymbol{\beta}'\mathbf{x}_{ij} + u_j - \kappa_s}{1}\right).$$

  - Therefore, the conditional or cluster-specific effects $\boldsymbol{\beta}$ of $\mathbf{x}_{ij}$ are greater than the marginal or population average effects $\boldsymbol{\beta}/\sqrt{\tau^2+1}$.

Slide 8

Cluster-specific versus population average effects



Slide 9

Multilevel random coefficient models

- Consider clustered longitudinal data with occasions i (level 1) nested in subjects j (level 2) in hospitals k (level 3)
- Example of a three-level random coefficient model:

$$y^*_{ijk} = [u^{(2)}_{0jk} + u^{(3)}_{0k}] + [\beta_1 + u^{(2)}_{1jk} + u^{(3)}_{1k}]x_{1ijk} + \beta_2 x_{2ijk} + \epsilon_{ijk}$$

  – $u^{(2)}_{0jk}$ and $u^{(3)}_{0k}$ are random intercepts at levels 2 and 3.
  – $u^{(2)}_{1jk}$ and $u^{(3)}_{1k}$ are random coefficients of x_{1ijk}.
  – The random coefficients have zero means and the fixed effect β_1 of x_{1ijk} represents the mean effect.
  – Random effects at the same level are correlated, $(u^{(2)}_{0jk}, u^{(2)}_{1jk})$ is bivariate normal.
- General three-level random coefficient model

$$y^*_{ijk} = \boldsymbol{\beta}'\mathbf{x}_{ijk} + \mathbf{u}^{(2)\prime}_{jk}\mathbf{z}^{(2)}_{ijk} + \mathbf{u}^{(3)\prime}_{jk}\mathbf{z}^{(3)}_{ijk} + \epsilon_{ijk}$$

Slide 10

Estimation

- Estimation of multilevel models with categorical responses, also known as generalised linear mixed models (GLMMs), is not easy because the likelihood does not generally have a closed form.
- Marginal Quasilikelihood (MQL) and Penalized Quasilikelihood (PQL) are approximate methods avaiblable in `MLwiN` and `HLM`.
  – Two versions are available, first and second order (MQL-1,MQL-2,PQL-1,PQL-2), the last being the best.
  – Even PQL-2 sometimes produces biased estimates, particularly when the clusters are small.
  – The methods do not provide a likelihood.
- Maximum likelihood estimation requires evaluation of integrals since the likelihood is marginal with respect to the random effects.
  – Numerical integration using Gauss-Hermite quadrature is used in `MIXOR/MIXNO` (two-level only), aML, `SAS PROC NLMIXED` (two-level only) and `gllamm`.
  – Adaptive quadrature is superior to 'ordinary quadrature' which sometimes doesn't work (e.g. large clusters, counts). This is available in `SAS PROC NLMIXED` (two-level only) and `gllamm`.
  – `HLM` provides a 6th order Laplace approximation for two-level models with dichotomous responses.

Slide 11

Cluster randomized trial of sex education

- Schools were randomised to receive sex education or not
- Assessments pre randomisation, 6 months and 18 months post randomisation
- One outcome is a question relating to 'Contraceptive self-efficacy':
  - "If my partner and I were about to have intercourse without either of us having mentioned contraception, it would be easy for me to produce a condom (if I brought one)"
  - The questions is answered in terms of five ordinal categories: 'not at all true of me', 'slightly true of me', 'somewhat true of me', 'mostly true of me', 'completely true of me'.
- The data are multilevel with responses (level 1) from 1184 pupils (level 2) from 46 schools (level 3).
- Only 570 pupils always responded, 400 responded on some occasions and 114 never responded.

Slide 12

Models

- Occasions t, subjects j, schools k
- Covariates
  - x_{1t} [Time] (0, 1, 3)
  - x_{2jk} [Treat] (yes=1,no=0)
  - x_{3tjk} [Treat] $\times$ [Time]
- Model the probability of exceeding a category s, $s = 1, 2, 3, 4$

  $$\text{logit}[\Pr(y_{tijk} > s)] = \beta_1 x_{1t} + \beta_2 x_{2jk} + \beta_3 x_{3tjk} + u_{jk}^{(2)} + u_k^{(3)} - \kappa_s$$
- Estimation using adaptive quadrature in `gllamm`:

```
gllamm use treat time treat_time, i(id school) /*
   */ link(ologit) family(binom) adapt
```

- Conditional and marginal probabilities:

```
gen u1 = 0
gen u2 = 0
gllapred p_cond, mu us(u) above(2)
gllapred p_marg, mu marg above(2)
```

Slide 13

Estimates

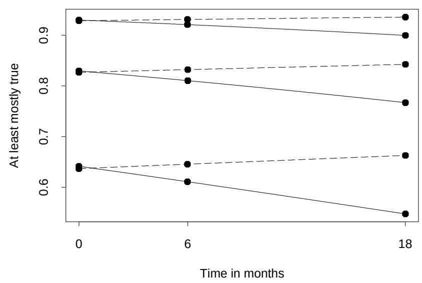
Parameter	Single-level model Est	(SE)	Two-level model Est	(SE)	Three-level model Est	(SE)
β_1 [Time]	-0.12	(0.06)	-0.13	(0.06)	-0.13	(0.06)
β_2 [Treat]	-0.05	(0.14)	-0.02	(0.19)	-0.02	(0.19)
β_3 [Time]×[Treat]	0.17	(0.08)	0.17	(0.09)	0.17	(0.09)
$\text{var}(u_{jk}^{(2)})$	–		2.03	(0.31)	2.03	(0.31)
$\text{var}(u_{k}^{(2)})$	–		–		0.00	(0.00)
κ_1	-3.54	(0.17)	-4.41	(0.23)	-4.41	(0.23)
κ_2	-2.43	(0.13)	-3.15	(0.19)	-3.15	(0.19)
κ_3	-1.18	(0.12)	-1.58	(0.16)	-1.58	(0.16)
κ_4	0.16	(0.12)	0.25	(0.15)	0.25	(0.15)
Log-likelihood	-2531		-2471		-2471	

Slide 14

Conditional relationships

- Probability of responding at least 'mostly true of me' (category 3)
- Relationship between the probability and occasion for the two treatment groups, when the random intercept is -1, 0 and 1:

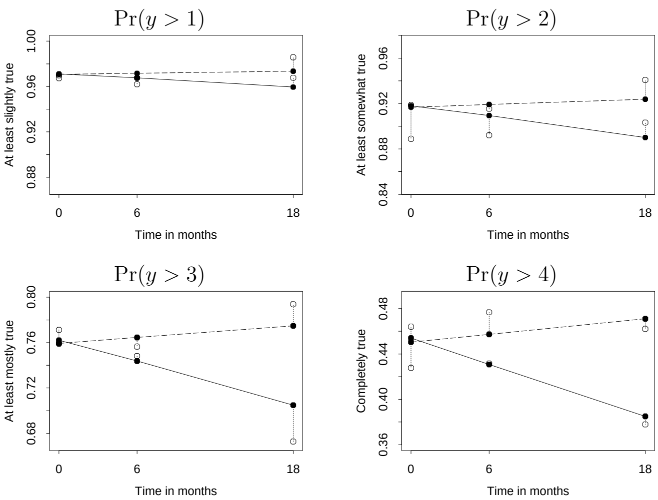
---- intervention group, —— control group



Slide 15

Observed and predicted marginal proportions

---- intervention group, —— control group, • predicted, ○ observed



Slide 16

II. Unordered categorical responses

- Only a small number of responses or 'categories' are possible, a, $a = 1, \cdots, A$.
- The categories cannot be ordered a priori.
- Examples:
  - Treatment decision: 'chemotherapy', 'surgery', 'none'
  - Health insurance choice: 'NHS', 'PPP', etc.
  - Method of birth control: 'pill', 'condom', etc.
  - Diagnosis: 'meningitis', 'influenza', 'common cold'
- Unordered categorical responses often correspond to a 'first choice' among a set of alternatives.

Slide 17

Random Utility Models

- Unobserved 'utility' U_i^a associated with each alternative $a = 1, ..., A$ for unit $i = 1, ..., N$
- Random utility models composed as

$$U_i^a \;=\; V_i^a + \epsilon_i^a$$

  - V_i^a is the linear predictor
  - ϵ_i^a is a residual term (independent over i and a)
- Alternative f is chosen if

$$U_i^f > U_i^g \text{ for all } g \neq f$$

ϵ_i^a independent Gumbel distributed

$$\Updownarrow$$

$$\Pr(f_i) \;=\; \frac{\exp(V_i^f)}{\Sigma_{a=1}^A \exp(V_i^a)}$$

[Conventional multinomial logit]

Slide 18

Covariate effects on the utilities

Linear predictor for unit i and alternative a:

$$V_i^a \;=\; m^a + \mathbf{g}^{a\prime}\mathbf{x}_i + \mathbf{b}'\mathbf{x}_i^a$$

- Covariates and parameters:
  - m^a alternative specific constants
  - $\mathbf{x}_i$ varies over subjects (but not alternatives) and has fixed effects $\mathbf{g}^a$ varying over alternatives
    Examples: Age of subject
  - $\mathbf{x}_i^a$ varies over alternatives (and possibly subjects) and has fixed effects $\mathbf{b}$ not varying over alternatives
    Example: Cost of treatment (could differ between countries)
- Identification:
  - Probability of choosing alternative 1 among alternatives 1, 2 and 3 can be expressed in terms of utility differences $\Pr(U^1 - U^2 > 0 \text{ and } U^1 - U^3 > 0)$
  - Therefore the location of V_i^a is arbitrary:

$$\frac{\exp(V_i^1)}{\Sigma_a \exp(V_i^a)} = \frac{\exp(V_i^1 + c_i)}{\Sigma_a \exp(V_i^a + c_i)}$$

  - Solution: Last alternative S serves as reference alternative, set $m^S = 0$ and $\mathbf{g}^S = \mathbf{0}$.

Slide 19

Multilevel models

- Consider three-level data with patients i (level 1) treated by doctors j (level 2) working in hospitals k (level 3).
- We can include random effects in the linear predictor:

$$\begin{aligned} V_{ijk}^a &= m^a + \gamma_{0jk}^{a(2)} + \gamma_{0j}^{a(3)} \\ &\quad + [\mathbf{g}^{a\prime} + \boldsymbol{\gamma}_{jk}^{a(2)\prime} + \boldsymbol{\gamma}_{k}^{a(3)\prime}]\mathbf{x}_{ijk} \\ &\quad + [\mathbf{b}' + \boldsymbol{\beta}_{jk}^{(2)\prime} + \boldsymbol{\beta}_{k}^{(3)\prime}]\mathbf{x}_{ijk}^a \end{aligned}$$

- Random intercepts: $\gamma_{0jk}^{a(2)}$ and $\gamma_{0k}^{a(3)}$
- Random Coefficients I: $\boldsymbol{\gamma}_{jk}^{a(2)}$ and $\boldsymbol{\gamma}_{k}^{a(3)}$ are alternative specific random coefficients for *subject*-specific covariates $\mathbf{x}_{ijk}$.
- Random Coefficients II: $\boldsymbol{\beta}_{jk}^{(2)}$ and $\boldsymbol{\beta}_{k}^{(3)}$ are random coefficients for *alternative*-specific covariates $\mathbf{x}_{ijk}^a$.

Slide 20

Use and abuse of antibiotics for API*

- Acute respiritory tract infection (API) can lead to pneumonia and death if not properly treated, but inappropriate frequent use of antibiotics can lead to drug resistance.
- In the 1990's the WHO introduced a program of case management for children under 5 in China.
- Doctor's antibiotic prescription was rated as 'abuse' if there were no clinical indicators:
  1. Abuse of serveral antibiotics
  2. Abuse of one antibiotic
  3. Correct use of antibiotics (reference-category)
- Data are multilevel with 2565 children i (level 1) treated by 134 doctors j (level 2) in 36 hospitals k (level 3).
- Covariates ($\mathbf{x}_{ijk}$) include
  – [Age] Age in years (0-5)
  – [Temp] Body temperature, centered at 36^{o}C
  – [Paymed] Pay for medication (yes=1, no=0)
  – [Selfmed] Self medication (yes=1, no=0)
  – [Wrdiag] Wrong diagnosis (yes=1, no=0)
  – [WHO] Hospital in WHO program (yes=1, no=0)
  – [DRed] Doctor's education (self-taught to med. school)

* Thanks to Min Yang for providing the data

Slide 21

Models

- Children i treated by doctors j working in hospitals k
- There are no alternative-specific covariates

$$V^a_{ijk} = m^a + \gamma^{a(2)}_{jk} + \gamma^{a(3)}_{j} + \mathbf{g}^{a\prime}\mathbf{x}_{ijk}$$

- Data:

```
doc child alt choice
1   1     1   0
1   1     2   1
1   1     3   0
1   2     1   0
1   2     2   0
1   2     3   1
```

- Estimation in `gllamm`

```
gen categ1 = alt == 1
gen categ2 = alt == 2
eq c1: categ1
eq c2: categ2
gllamm alt age temp ... , i(doc hosp)    /*
  */ nrf(2 2) eqs(c1 c2 c1 c2)           /*
  */ link(mlogit) family(binom)          /*
  */ expanded(child choice m) basecat(3)
```

Slide 22

Estimates

	Abuse several		Abuse one	
Parameter	Est	(SE)	Est	(SE)
g^a_0 [Cons]	-1.64	(0.49)	0.23	(0.32)
g^a_1 [Age]	0.09	(0.09)	0.19	(0.08)
g^a_2 [Temp]	-0.27	(0.13)	-1.01	(0.12)
g^a_3 [Paymed]	0.91	(0.41)	0.30	(0.31)
g^a_4 [Selfmed]	-0.78	(0.29)	-0.42	(0.24)
g^a_5 [Wrdiag]	1.80	(0.26)	2.08	(0.23)
g^a_6 [WHO]	–		–	
g^a_7 [DRed]	–		–	
Doctor-level variances				
$\mathrm{var}(\gamma^{a(2)}_0)$	0.43	(0.27)	0.51	(0.26)
$\mathrm{Cov}(\gamma^{1(2)}_0, \gamma^{2(2)}_0)$		-0.47 (0.15)		
Hospital-level variances				
$\mathrm{var}(\gamma^{a(3)}_0)$	2.50	(0.93)	0.23	(0.18)
$\mathrm{Cov}(\gamma^{1(3)}_0, \gamma^{2(3)}_0)$		0.68 (0.31)		
Log-likelihood		-730.6		

Slide 23

More Estimates

	Abuse several		Abuse one	
Parameter	Est	(SE)	Est	(SE)
g_0^a [Cons]	-5.72	(0.99)	-0.23	(0.55)
g_1^a [Age]	0.07	(0.09)	0.17	(0.08)
g_2^a [Temp]	-0.27	(0.13)	-0.96	(0.12)
g_3^a [Paymed]	0.92	(0.40)	0.12	(0.32)
g_4^a [Selfmed]	-0.86	(0.29)	-0.49	(0.24)
g_5^a [Wrdiag]	1.85	(0.26)	2.08	(0.23)
g_6^a [WHO]	-2.40	(0.62)	-0.88	(0.33)
g_7^a [DRed]	-0.62	(0.17)	0.08	(0.11)
Doctor-level variances				
$\mathrm{var}(\gamma_0^{a(2)})$	0.46	(0.28)	0.43	(0.22)
$\mathrm{Cov}(\gamma_0^{1(2)}, \gamma_0^{2(2)})$		-0.44 (0.13)		
Hospital-level variances				
$\mathrm{var}(\gamma_0^{a(3)})$	0.88	(0.45)	0.11	(0.12)
$\mathrm{Cov}(\gamma_0^{1(3)}, \gamma_0^{2(3)})$		0.31 (0.20)		
Log-likelihood		-716.2		

Slide 24

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