Multilevel and Longitudinal Modelling

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OUTLINE

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III. Multilevel logistic regression (slide 65)

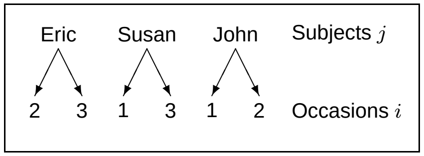
IV. Longitudinal data and alternatives to multilevel modelling (slide 95)

I. Random intercept models

- Clustered data, unobserved heterogeneity and dependence
- Random intercept models
- Intraclass correlation
- Example: GHQ test-retest data
- Estimation, testing and confidence intervals
- Empirical Bayes prediction and shrinkage
- Fixed versus random effects

Clustered data

- An important assumption in linear regression and logistic regression is that units (usually people) are independent (given covariates x)
- An important violation is due to clustered data with responses y_{ij} on units i grouped in clusters j:
  - Students i clustered in schools j
  - Siblings i clustered in families j
  - Repeated observations i clustered in people j (longitudinal, repeated measures, or panel data)



- General terms: level-1 units i clustered in level-2 units j

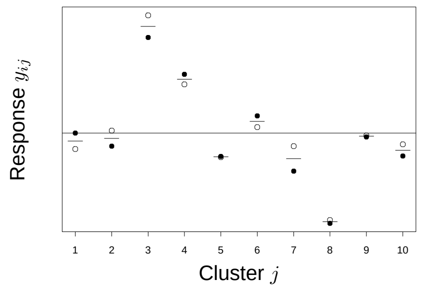
Unobserved heterogeneity

- Could not hope to explain all variability between clusters (e.g. schools) using observed covariates x
  - For instance, the school atmosphere, parents' involvement, teachers' enthusiasm and competence, etc., cannot all be measured
- Therefore there is **unobserved heterogeneity** (= unexplained variability) between clusters
- Means that two observations in same cluster are correlated and more similar than observations in different clusters
  - Students in one school tend to have better test results, even after controlling for covariates, than students in another school

Heterogeneity and dependence

- Example: No covariates, two units $i = 1, 2$ per cluster j with responses y_{ij}:

$$y_{ij} \;=\; \beta + \xi_{ij}, \quad \xi_{ij} \text{ is a residual}$$



- ● is y_{1j}
- ○ is y_{2j}
- – is the mean $\frac{1}{2}(y_{1j} + y_{2j})$

- Residuals ξ_{ij} for same cluster usually have same sign, corresponding to **within-cluster correlations** or dependence

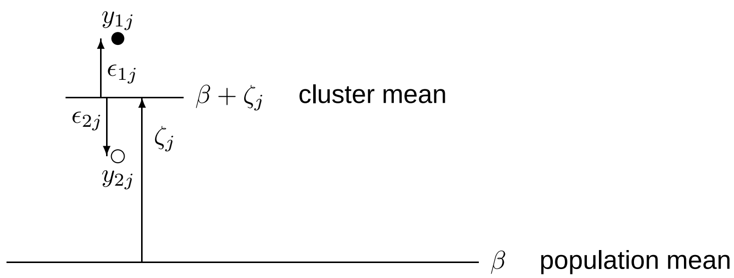
Variance-components model

- Model between-cluster heterogeneity:

$$y_{ij} \;=\; \beta + \underbrace{\zeta_j + \epsilon_{ij}}_{\xi_{ij}}$$

  - Total residual ξ_{ij} split into level-2 residual ζ_j (shared by all members of cluster) and level-1 residual (unit-specific) ϵ_{ij}
  - ζ_j, **random intercept** for cluster j
    - ◇ deviation of true cluster-mean $\beta + \zeta_j$ from overall mean β
    - ◇ independent of $\zeta_{j'}$ for other clusters j'
    - ◇ mean zero and variance ψ (a model parameter)
  - ϵ_{ij}, the **level-1 residual**
    - ◇ deviation of y_{ij} from its true cluster mean $\beta + \zeta_j$
    - ◇ independent of $\epsilon_{i'j'}$ for other i' or j' and of ζ_j and $\zeta_{j'}$
    - ◇ mean zero and variance θ (a model parameter)

Illustration of variance components model



Variance components

- Total residual or error:

$$\xi_{ij} \;=\; \zeta_j + \epsilon_{ij}$$

  - Can view ζ_j and ϵ_{ij} as **error components**

- Total residual variance:

$$\text{var}(\xi_{ij}) \;=\; \text{var}(\zeta_j) + \text{var}(\epsilon_{ij}) \;=\; \overbrace{\psi}^{\text{between}} + \overbrace{\theta}^{\text{within}}$$

  - Variances add up because ζ_j and ϵ_{ij} are independent
  - ψ and θ are therefore **variance components**

- Total variance of y_{ij}:

$$\text{var}(y_{ij}) \;=\; \text{var}(\beta + \xi_{ij}) = \text{var}(\xi_{ij}) = \psi + \theta$$

Conditional independence

- Responses conditionally independent **given random intercept**
- Zero covariance and correlation between measurements on two units i and i', given the random intercept ζ_j,

$$\text{Cor}(y_{ij}, y_{i'j}|\zeta_j) \;=\; 0$$

Intraclass correlation

- Covariance between responses on two units i and i' for the same cluster j (**not conditioning** on ζ_j)

$$\text{Cov}(y_{ij}, y_{i'j}) = \text{E}[(y_{ij} - \underbrace{\beta}_{\text{E}(y_{ij})})(y_{i'j} - \underbrace{\beta}_{\text{E}(y_{i'j})})] = \text{E}[(\zeta_j + \epsilon_{ij})(\zeta_j + \epsilon_{i'j})] = \text{E}[\zeta_j^2] = \psi$$

- Corresponding **intraclass correlation** is covariance divided by product of standard deviations

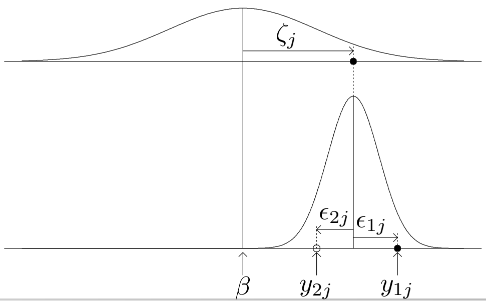
$$\text{Cor}(y_{ij}, y_{i'j}) = \frac{\text{Cov}(y_{ij}, y_{i'j})}{\sqrt{\text{Var}(y_{ij})}\sqrt{\text{Var}(y_{i'j})}} = \frac{\psi}{\sqrt{\psi+\theta}\sqrt{\psi+\theta}} = \frac{\psi}{\psi+\theta} = \rho$$

- Proportion of total variance shared among units in same cluster and therefore due to clusters (similar to coefficient of determination R^2)

$$\rho \;=\; \frac{\text{Var}(\zeta_j)}{\text{Var}(y_{ij})} = \frac{\psi}{\psi+\theta}$$

Distributional assumptions

- Assume that $\zeta_j \sim \text{N}(0, \psi)$
- Assume that $\epsilon_{ij} \sim \text{N}(0, \theta)$
- Hierarchical, two-stage model, reflecting two-stage sampling:
  - $\zeta_j \sim \text{N}(0, \psi) \Longrightarrow$ determines $\beta + \zeta_j$
  - $\epsilon_{ij} \sim \text{N}(0, \theta) \Longrightarrow$ determines $y_{ij} \;=\; \beta + \zeta_j + \epsilon_{ij}$



Parameter estimation (β, ψ, θ)

- Maximum likelihood estimation (ML)
  - If variances were known, would use GLS (generalised least squares) $\Rightarrow$ IGLS (Iterative GLS), iterating between estimation of fixed and random part
  - EM (Expectation-Maximization) algorithm: Treat random effects as missing values
- Restricted maximum likelihood estimation (REML)
  - ML gives downward biased estimate of random intercept variance
  - If cluster size is constant, $n_j = n$, REML gives unbiased estimates (if estimates allowed to be negative)
  - REML is ML applied to ‘residuals’
- Software: `MLwiN`, `HLM`, SPSS: `MIXED`, Stata: `xtmixed`, SAS: `MIXED`, R: `lmer` (all give identical estimates)

Hypothesis testing and confidence intervals

- Inference for β
  - **Wald test**: Use estimated standard error $\widehat{\text{SE}}(\widehat{\beta})$ for test statistic (and confidence interval)

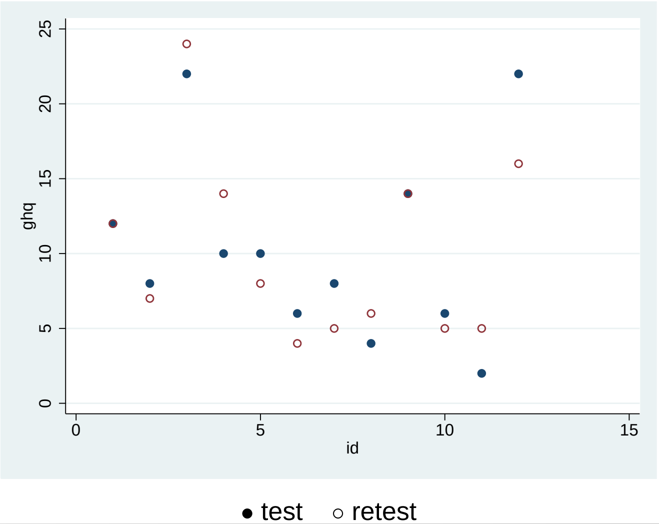
$$H_0 : \beta = \mu_0, \qquad z = \frac{\widehat{\beta} - \mu_0}{\widehat{\text{SE}}(\widehat{\beta})}$$

- Test for zero between-cluster variance $H_0 : \psi = 0$
  - **Likelihood ratio test** (DO NOT USE WALD TEST)
    - ◇ Compare log-likelihood L_1 for random-intercept model with log-likelihood L_0 for ordinary regression model (no ζ_j)
    - ◇ Test statistic $G^2 = 2(L_1 - L_0)$
    - ◇ Asymptotic sampling distribution under H_0 not $\chi^2(1)$ because null hypothesis is on boundary of parameter space since $\psi \geq 0$
    - ◇ Solution: assume $\chi^2(1)$ distribution, but divide p-value by 2

Example: GHQ test-retest data

- General Health Questionnaire (GHQ) to measure psychological distress
- Sum of 12 items, each scored 0,1, or 2
- Completed twice by 12 clinical psychology students, 3 days apart
- Variables:
  - Subject id j
  - Occasion (1:test, 2:retest) i
  - GHQ score y_{ij}

Graph for GHQ data



Maximum likelihood estimates for GHQ data

	Est	(SE)
Fixed part		
β	10.17	(1.68)
Random part		
$\sqrt{\psi}$	5.65	
$\sqrt{\theta}$	1.91	
Log-likelihood	-67.13	

Exercises: GHQ data

- Calculate the estimated intraclass correlation
- Consider the Pearson correlation between test and retest. Is this different than the intraclass correlation? If so, why?

Assigning values to random effects: Empirical Bayes prediction

- ζ_j is a **residual** like ϵ_{ij}
- ζ_j is a random variable, not a model parameter
- As in ordinary regression, sometimes want to **predict** residuals
- Reasons for predicting ζ_j:
  - Residual diagnostics
  - Inference for cluster-mean $\beta + \zeta_j$ or ζ_j
    - Measurement (e.g., GHQ): $\beta + \zeta_j$ is "true score"
    - Institutional performance: ζ_j is "value added"
  - Model interpretation

Assigning values to random effects: Empirical Bayes prediction

- Treat parameter estimates $\widehat{\beta}$, $\widehat{\psi}$ and $\widehat{\theta}$, as known parameter values
- For cluster j, empirical Bayes combines
  1. **Prior distribution** of ζ_j, knowledge about ζ_j before seeing data for the cluster

     $$\text{Prior}(\zeta_j) \qquad \left[\text{normal density } g(0, \widehat{\psi})\right]$$

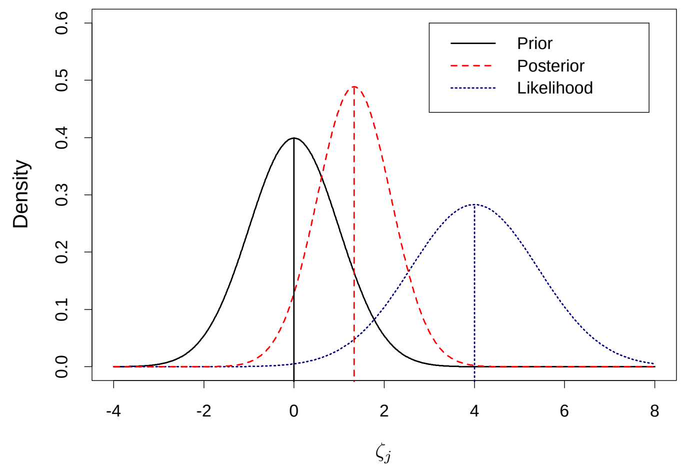
  2. **Likelihood**, knowledge about ζ_j provided by the data $\mathbf{y}_j$ (and $\mathbf{X}_j$)

     $$\text{Likelihood}(\mathbf{y}_j|\zeta_j) \qquad \left[\prod_{i=1}^{n_j} g(\widehat{\beta} + \zeta_j, \widehat{\theta})\right]$$

- To obtain posterior distribution of random intercept (Bayes Theorem)

$$\text{Posterior}(\zeta_j|\mathbf{y}_j) \propto \text{Prior}(\zeta_j) \times \text{Likelihood}(\mathbf{y}_j|\zeta_j)$$

Empirical Bayes prediction (cont'd)



- Empirical Bayes prediction $\widetilde{\zeta}_j = 1.33$ is **mean of posterior distribution**

Fixed instead of random effects of clusters

- Can view clusters as categories of categorical explanatory variable
- **Fixed effects of cluster**: dummy variable d_{mj} for cluster j (no intercept)

$$y_{ij} = \overbrace{\sum_{m=1}^{J} \alpha_m d_{mj}}^{\alpha_j} + \epsilon_{ij}, \quad d_{mj} = \begin{cases} 1 & \text{if } m = j \\ 0 & \text{if } m \neq j \end{cases} \quad \epsilon_{ij} \sim \mathrm{N}(0, \theta)$$

  - α_j are fixed parameters, representing clusters' population means
  - ϵ_{ij} is a random error term, representing within-cluster variability
- **Random effects of cluster**:

$$y_{ij} = \beta + \zeta_j + \epsilon_{ij}, \qquad \zeta_j \sim \mathrm{N}(0, \psi), \quad \epsilon_{ij} \sim \mathrm{N}(0, \theta)$$

  - β is a fixed parameter, the **population mean**
  - ζ_j and ϵ_{ij} are random error terms

Fixed effects approach for GHQ data (cont'd)

	FE	EST	(SE)	RE	EB	(SE)
Fixed part	α_1	12	(1.35)	$\beta+\zeta_1$	11.9	(1.32)
	α_2	7.5	(1.35)	$\beta+\zeta_2$	7.6	(1.32)
	α_3	23.0	(1.35)	$\beta+\zeta_3$	22.3	(1.32)
	α_4	12.0	(1.35)	$\beta+\zeta_4$	11.9	(1.32)
	α_5	9.0	(1.35)	$\beta+\zeta_5$	9.1	(1.32)
	α_6	5.0	(1.35)	$\beta+\zeta_6$	5.3	(1.32)
	α_7	6.5	(1.35)	$\beta+\zeta_7$	6.7	(1.32)
	α_8	5.0	(1.35)	$\beta+\zeta_8$	5.3	(1.32)
	α_9	14.0	(1.35)	$\beta+\zeta_9$	13.8	(1.32)
	α_{10}	5.5	(1.35)	$\beta+\zeta_{10}$	5.8	(1.32)
	α_{11}	3.5	(1.35)	$\beta+\zeta_{11}$	3.9	(1.32)
	α_{12}	19.0	(1.35)	$\beta+\zeta_{12}$	18.5	(1.32)
Random part	θ	3.7				

- 13 parameters (θ and 12 α_j) for fixed-effects model, compared with 3 parameters (θ, β, ψ) for random-effects model
- In random-effects model, use **empirical Bayes** to assign values to cluster means $\beta + \zeta_j$

Maximum likelihood estimation of cluster-specific effects

- Estimated coefficients $\widehat{\alpha}_j$ of dummies are ML estimates of $\beta + \zeta_j$
  - **Maximum likelihood estimates** of ζ_j, maximum of Likelihood$(\mathbf{y}_j|\zeta_j)$ with $\widehat{\beta}$ treated as known
  - Also called OLS (Ordinary Least Squares) estimates
  - Simply the cluster means of the estimated total residuals $\widehat{\xi}_{ij}$

$$\widehat{\xi}_{ij} = y_{ij} - \widehat{\beta} = \widehat{\zeta_j + \epsilon_{ij}}$$

$$\widehat{\zeta}_j^{\mathrm{ML}} = \frac{1}{n_j} \sum_{i=1}^{n_j} \widehat{\xi}_{ij}$$

Shrinkage

- Empirical Bayes prediction of random intercept can be written as

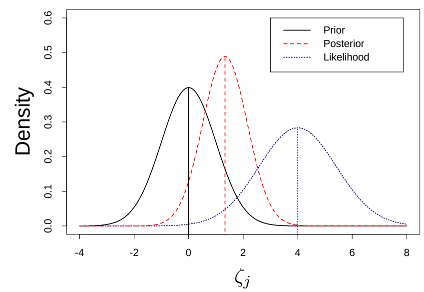
$$\widetilde{\zeta}_j^{\mathrm{EB}} = \widehat{R}_j \widehat{\zeta}_j^{\mathrm{ML}}, \qquad \widehat{R}_j = \frac{\widehat{\psi}}{\widehat{\psi} + \widehat{\theta}/n_j}$$

  - $\widehat{R}_j$ is estimated 'reliability' of ML estimator (true score variance divided by total variance of $\widehat{\zeta}_j^{\mathrm{ML}}$)
  - $\widehat{R}_j$ is **shrinkage factor**, shrinking prediction towards 0 (mean of prior) since $0 \leq \widehat{R}_j \leq 1$
  - More shrinkage (i.e. greater influence of prior) if
    - Small random intercept variance $\widehat{\psi}$ (informative prior)
    - Large level-1 residual variance $\widehat{\theta}$ (non-informative data)
    - Small cluster size n_j (non-informative data)

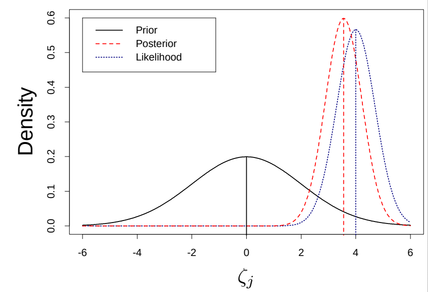
Illustration: Shrinkage

- Cluster with $n_j = 2$ units
- Predicted total residuals $\widehat{\xi}_{1j} = 3$ and $\widehat{\xi}_{2j} = 5$

Much shrinkage:
$\widehat{\psi} = 1, \widehat{\theta} = 4 \Rightarrow \widehat{R}_j = 0.33$



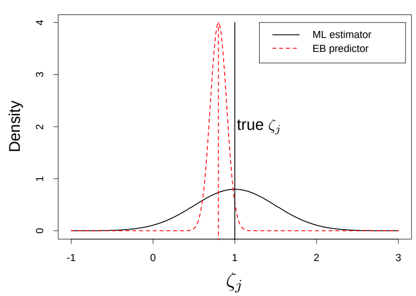
Little shrinkage:
$\widehat{\psi} = 4, \widehat{\theta} = 1 \Rightarrow \widehat{R}_j = 0.89$



Bias/precision trade-off

- EB prediction conditionally biased towards zero unlike ML: For a given cluster, mean EB prediction (over repeated samples of units) closer to zero than true random intercept
- EB has smaller prediction error variance (mean squared error) than ML, i.e. more accurate, especially for small clusters

Example:
Sampling
Distributions



- Also called 'Best Linear Unbiased Predictor' (BLUP)

"Borrowing strength" or partial pooling

- EB for cluster j 'borrows strength' from other clusters
- Estimate of true cluster mean $\beta + \zeta_j$ is:
  - ML:

$$\widehat{\beta} + \widehat{\zeta}_j^{\mathrm{ML}} = \widehat{\beta} + \frac{1}{n_j}\sum_{i=1}^{n_j}(y_{ij} - \widehat{\beta}) = \widehat{\beta} + (\bar{y}_{\cdot j} - \widehat{\beta}) = \bar{y}_{\cdot j}$$

  $\Longrightarrow$ sample mean of cluster j

  - EB:

$$\widehat{\beta} + \widetilde{\zeta}_j^{\mathrm{EB}} = \widehat{\beta} + \widehat{R}_j \widehat{\zeta}_j^{\mathrm{ML}} = \widehat{\beta} + \widehat{R}_j(\bar{y}_{\cdot j} - \widehat{\beta}) = (1 - \widehat{R}_j)\widehat{\beta} + \widehat{R}_j \bar{y}_{\cdot j}$$

  $\Longrightarrow$ weighted mean of:
  sample mean of cluster j and $\widehat{\beta}$, estimate based on all clusters

Fixed versus random effects

Issue	Fixed effects	Random effects
Inference for population of clusters	No $-$	Yes $+$
Number of clusters required	Any number $+$	At least 10 or 20 $-$
Assumptions	None for distribution of intercepts $+$	Intercepts normal, constant variance, etc. $-$
Inference for individual clusters	Yes $+$	Yes, empirical Bayes $+$
Cluster sizes required	Any sizes if many ≥ 2, but overfitting if small $\pm$	Any sizes if many ≥ 2 $+$
Parsimony	A parameter α_j for each cluster $-$	One variance parameter ψ for all cluster $+$

- **Note:** Further issues if there are covariates and for generalized linear mixed models

Exercise: Fixed versus random

- In each situation below, should fixed or random effects be used?

1. Math achievement, 3 schools, 30 to 40 students per school
2. Reading test, 43 countries, about 2000 students per country
3. Longitudinal data on 20 subjects, 3 observations per subject
4. Blood pressure, 10 treatment groups, 20 patients per group
5. Depression, 15 therapists, 3-15 patients per therapist

II. Random coefficient models

- Random intercept model with covariates
- Example: Georgian birthweights
- Between effects, within effects and endogeneity
- Random coefficients

Random intercept model with covariate

- Add covariate to variance components model:

$$y_{ij} = \underbrace{\beta_1 + \beta_2 x_{ij}}_{\text{fixed part}} + \underbrace{\zeta_j + \epsilon_{ij}}_{\text{random part}}$$

- Intercept varies between clusters:

$$y_{ij} = \underbrace{\beta_1 + \zeta_j}_{\substack{\text{intercept} \\ \text{for cluster } j}} + \beta_2 x_{ij} + \epsilon_{ij}$$

Assumptions for random intercept model with covariate

- Assumptions for ϵ_{ij} and ζ_j:
  - $E(\epsilon_{ij}|\zeta_j, \mathbf{X}_j) = 0$
    - $\Rightarrow$ Cov$(\epsilon_{ij}, \mathbf{X}_j) = 0$ [level-1 exogeneity]
    - $\Rightarrow$ variance decomposition
  - ϵ_{ij} independent over units i and clusters j
    $\Rightarrow$ conditional independence of responses given random intercept
  - $E(\zeta_j|\mathbf{X}_j) = 0$
    $\Rightarrow$ Cov$(\zeta_j, \mathbf{X}_j) = 0$ [level-2 exogeneity]
  - ζ_j independent for different j
    $\Rightarrow$ independent clusters in likelihood
- Distributional assumptions (for maximum likelihood):
  - ϵ_{ij} normal with zero mean and variance θ
  - ζ_j normal with zero mean and variance ψ

Regression lines

- Population averaged or **marginal** regression line (mean over population of clusters and populations of units within clusters)

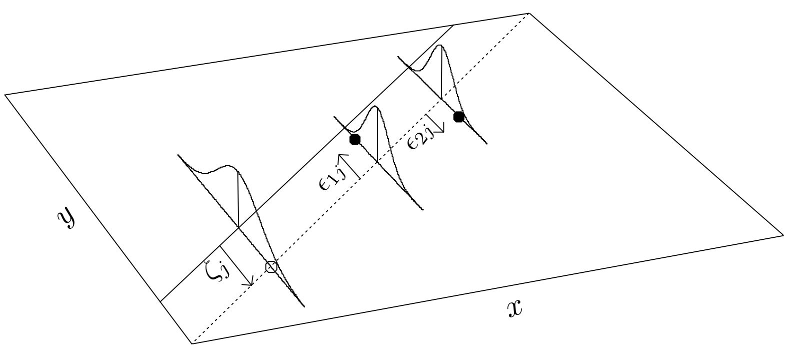
$$\mathrm{E}(y_{ij}|x_{ij}) \;=\; \beta_1 + \beta_2 x_{ij}$$

- Cluster-specific or **conditional** regression line (mean over population of units within cluster j)

$$\begin{aligned}\mathrm{E}(y_{ij}|x_{ij}, \zeta_j) &= \beta_1 + \beta_2 x_{ij} + \zeta_j \\ &= (\beta_1 + \zeta_j) + \beta_2 x_{ij}\end{aligned}$$

  - ψ is variance between cluster-specific intercepts $\beta_1 + \zeta_j$
  - θ is variance of y_{ij} around cluster-specific regression lines

Illustration of random intercept model with covariate



Example: Georgia birthweights

- 878 mothers of five children in Georgia, USA:
  - Child's birth weight in grams y_{ij}
  - Mother's age at the time of the child's birth x_{ij}
- Random intercept model:

$$y_{ij} \;=\; \beta_1 + \beta_2 x_{ij} + \zeta_j + \epsilon_{ij}$$

  - With the usual assumptions stated on slide 33

Estimates for Georgia birthweights (cont'd)

	with age		without age	
	Est	(SE)	Est	(SE)
Fixed part				
β_1	2785.2	(45.2)	3156.3	(14.1)
β_2 [age]	17.1	(2.0)		
Random part				
$\sqrt{\psi}$	354.6		368.4	
$\sqrt{\theta}$	434.2		435.5	
Log-likelihood	$-$33535.7		$-$33572.3	

Between and within-cluster covariates

- Covariates may vary
  - Between clusters, e.g., mother's own birthweight
  - Within clusters, e.g., children's parity (birth order) 1,2,3,4,5
  - Both between and within clusters, e.g., mother's age at birth
    - **Between-cluster variability**: Standard deviation of cluster mean age around overall mean is 3.7
    - **Within-cluster variability**: Standard deviation of age around cluster means is 2.8
    - **Overall variability**: Conventional standard deviation (ignoring clustering) is 4.6

Between and within-cluster effects of covariates

- Previous model:

$$y_{ij} \;=\; \beta_1 + \beta_2 x_{ij} + \zeta_j + \epsilon_{ij}$$

- Coefficient β_2 represents difference in mean birth weight for children whose mothers differ in age by one year
- Two types of comparisons or effects:
  - **Within-mother effect**:
    Same mother, children born at different times (ages)
  - **Between-mother effect**:
    Different mothers giving birth at different ages
- Model assumes that both effects are the same

Between and within cluster effects

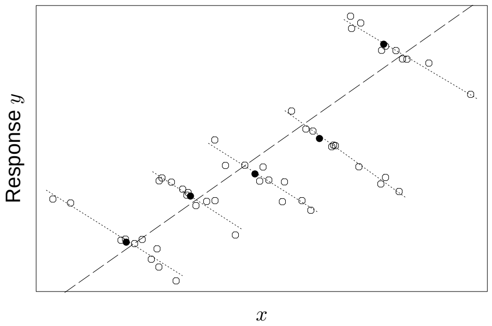
- **Between effect**: Take cluster average of random intercept model

$$\begin{aligned} \frac{1}{n_j}\sum_{i=1}^{n_j} y_{ij} &= \frac{1}{n_j}\sum_{i=1}^{n_j}[\beta_1 + \beta_2 x_{ij} + \zeta_j + \epsilon_{ij}] \\ \bar{y}_{\cdot j} &= \beta_1 + \beta_2 \bar{x}_{\cdot j} + \underbrace{\zeta_j + \bar{\epsilon}_{\cdot j}}_{e_j} \end{aligned}$$

- **Within effect**: Subtract cluster average random intercept model from random intercept model

$$\begin{aligned} y_{ij} &= [\beta_1 + \beta_2 x_{ij} + \zeta_j + \epsilon_{ij}] \\ -\bar{y}_{\cdot j} &= -[\beta_1 + \beta_2 \bar{x}_{\cdot j} + \zeta_j + \bar{\epsilon}_{\cdot j}] \\ \hline y_{ij} - \bar{y}_{\cdot j} &= \beta_2 (x_{ij} - \bar{x}_{\cdot j}) + \underbrace{\epsilon_{ij} - \bar{\epsilon}_{\cdot j}}_{e_{ij}} \end{aligned}$$

Illustration of different between and within-effects



- Hollow circles: individual units (x_{ij}, y_{ij})
- Dotted lines: within-cluster regression, slope is within-cluster effect
- Solid circles: cluster means $(\bar{x}_{\cdot j}, \bar{y}_{\cdot j})$
- Dashed line: between-cluster regression, slope is between-cluster effect
- Simpson's paradox, cluster-level confounding, **ecological fallacy**

Between and within-cluster estimates for Georgia birthweights

	Between		Within	
	Est	(SE)	Est	(SE)
Fixed part				
β_1	2499.1	(80.7)	2900.1	(51.1)
β_2 [age]	30.4	(3.7)	11.8	(2.3)

- Estimated between-effect much larger than within-effect
- Advantage of clustered data:
  Can distinguish between different kinds of effects!

Exercise: Between and within-effects

- Explain why you think there is a difference between the within and between-effects of mother's age on birth weight

Cluster-level confounding and endogeneity

- Random intercept model (equal between and within-cluster effects)

$$\begin{aligned} y_{ij} &= \beta_1 + \beta_2 x_{ij} + \zeta_j + \epsilon_{ij} \\ &= \beta_1 + \beta_2(x_{ij} - \bar{x}_{\cdot j}) + \beta_2 \bar{x}_{\cdot j} + \zeta_j + \epsilon_{ij} \end{aligned}$$

- Random intercept model assumes exogenous covariate (important if β_2 interpreted as causal effect of x_{ij} on y_{ij})
  - x_{ij} uncorrelated with ζ_j (no cluster-level confounding)
    - $\bar{x}_{\cdot j}$ uncorrelated with ζ_j
    - Assumption not made in within-cluster regression
      $y_{ij} - \bar{y}_{\cdot j} = \beta_2(x_{ij} - \bar{x}_{\cdot j}) + \epsilon_{ij} - \bar{\epsilon}_{\cdot j}$
  - x_{ij} uncorrelated with ϵ_{ij} (no unit-level confounding)
    - $(x_{ij} - \bar{x}_{\cdot j})$ uncorrelated with ϵ_{ij}
- Within-cluster estimate not subject to cluster-level confounding – closer to causal effect?

Allowing and testing for endogeneity

- Concern about bias due to correlation between ζ_j and x_{ij} (especially among economists who call this **endogeneity**)
  - Use within-effect estimator or modify random intercept model:

$$y_{ij} = \beta_1 + \beta_{2w}(x_{ij} - \bar{x}_{\cdot j}) + \beta_{2b}\bar{x}_{\cdot j} + \zeta_j + \epsilon_{ij}$$

    - β_{2w} is within-effect and β_{2b} is between-effect
  - If Cor$(x_{ij}, \zeta_j) \neq 0$
    - $\widehat{\beta}_{2b}$ inconsistent since Cor$(\bar{x}_{\cdot j}, \zeta_j) \neq 0$
    - $\widehat{\beta}_{2w}$ consistent since Cor$((x_{ij} - \bar{x}_{\cdot j}), \zeta_j) = 0$ and Cor$((x_{ij} - \bar{x}_{\cdot j}), \bar{x}_{\cdot j}) = 0$
  - Test of $H_0: \beta_{2w} = \beta_{2b}$, highly significant, $p < 0.001$
  - This test is equivalent to famous Hausman test in econometrics

Fixed instead of random effects of clusters

- Regression with dummy variables d_{mj} for each cluster (and no intercept) – ANCOVA model

$$y_{ij} = \overbrace{\sum_{m=1}^{J} \alpha_m d_{mj}}^{\alpha_j} + \beta_2 x_{ij} + \epsilon_{ij}, \quad d_{mj} = \begin{cases} 1 & \text{if } m = j \\ 0 & \text{if } m \neq j \end{cases}$$

  - Any between-cluster covariate z_j or $\bar{x}_{\cdot j}$ completely collinear with set of dummy variables, i.e., can be written as linear combination of dummy variables:

$$z_j = \sum_{m=1}^{J} z_m d_{mj} \qquad x_{\cdot j} = \sum_{m=1}^{J} x_{\cdot m} d_{mj}$$

    - Cannot include between-cluster covariates
    - **Estimate of β_2 is within-effect**; between-effect absorbed in α_1 to α_J

Fixed versus random effects revisited

Issue	**Fixed effects**		**Random effects**	
Inference for population of clusters	No	–	Yes	+
Number of clusters required	Any number	+	At least 10 or 20	–
Assumptions	None for distribution of intercepts	+	Intercepts normal, constant variance, etc.	–
Effects of cluster-level covariates	No	–	Yes	+
Inference for individual clusters	Yes	+	Yes, Empirical Bayes	+
Cluster sizes required	Any sizes if many ≥ 2, but overfitting if small	$\pm$	Any sizes if many ≥ 2	+
Parsimony	A parameter α_j for each cluster	–	One variance parameter ψ for all cluster	+
Within-cluster effects of covariates	Yes	+	Only with extra work	–

Random coefficient models

- Not only the overall level of the response (intercept) can vary between clusters, but also the slopes of within-cluster covariates
- Simple example:

$$\begin{aligned} y_{ij} &= \overbrace{\beta_1 + \zeta_{1j}}^{\text{intercept}} + \overbrace{(\beta_2 + \zeta_{2j})}^{\text{slope}} x_{ij} + \epsilon_{ij} \\ &= \underbrace{\beta_1 + \beta_2 x_{ij}}_{\text{fixed part}} + \underbrace{\zeta_{1j} + \zeta_{2j} x_{ij} + \epsilon_{ij}}_{\text{random part}} \end{aligned}$$

  - ζ_{1j} is random intercept: Deviation of cluster-specific intercept from mean intercept
  - ζ_{2j} is random slope: Deviation of cluster-specific slope from mean slope

Assumptions for random coefficient models

- Exogeneity assumptions analogous to random intercept model
- Distributional assumptions (for maximum likelihood):
  - ϵ_{ij} normal with zero mean and variance θ
  - (ζ_{1j}, ζ_{2j}) bivariate normal with zero means and unstructured covariance matrix (variances ψ_{11} and ψ_{22} and covariance ψ_{21})

Regression lines

- Population averaged or **marginal** regression line (mean over population of clusters and populations of units within clusters)

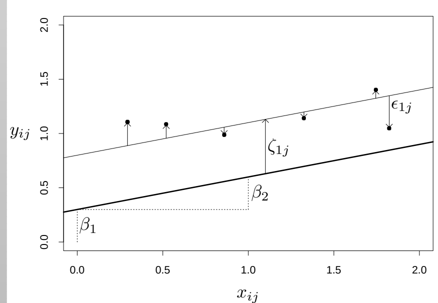
$$\mathrm{E}(y_{ij}|x_{ij}) = \beta_1 + \beta_2 x_{ij}$$

- Cluster-specific or **conditional** regression line (mean over population of units within cluster j)

$$\begin{aligned}\mathrm{E}(y_{ij}|x_{ij}, \zeta_{1j}, \zeta_{2j}) &= \beta_1 + \beta_2 x_{ij} + \zeta_{1j} + \zeta_{2j} x_{ij} \\ &= (\beta_1 + \zeta_{1j}) + (\beta_2 + \zeta_{2j}) x_{ij}\end{aligned}$$

Illustration of random coefficient model

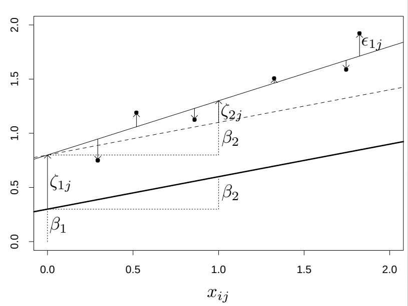
Random intercept model



$$y_{ij} = (\beta_1 + \zeta_{1j}) + \beta_2 x_{ij} + \epsilon_{ij}$$

ζ_{1j}: vertical shift

Random coefficient model



$$y_{ij} = (\beta_1 + \zeta_{1j}) + (\beta_2 + \zeta_{2j}) x_{ij} + \epsilon_{ij}$$

ζ_{1j}: vertical shift at $x_{ij} = 0$

Parameters of random part

- Four unique parameters for random part:
  - Unstructured covariance matrix of intercepts ζ_{1j} and slopes ζ_{2j}:

$$\begin{bmatrix} \mathrm{Var}(\zeta_{1j}) & \mathrm{Cov}(\zeta_{1j}, \zeta_{2j}) \\ \mathrm{Cov}(\zeta_{2j}, \zeta_{1j}) & \mathrm{Var}(\zeta_{2j}) \end{bmatrix} = \begin{bmatrix} \psi_{11} & \psi_{12} \\ \psi_{21} & \psi_{22} \end{bmatrix}, \qquad \psi_{21} = \psi_{12}$$

  - Variance of level-1 residuals ϵ_{ij}: θ
- Easier to interpret standard deviations $\sqrt{\psi_{11}}$, $\sqrt{\psi_{22}}$, $\sqrt{\theta}$ and correlation ρ_{21}

$$\rho_{21} = \frac{\psi_{21}}{\sqrt{\psi_{11}\psi_{22}}}$$

Two-stage formulation

- Raudenbush and Bryk (R&B) define multilevel model in stages:
  - **Level-1 model** with cluster-specific coefficients and unit-specific covariates:

$$y_{ij} = \beta_{0j} + \beta_{1j}x_{ij} + r_{ij}$$

  - **Level-2 models** for cluster-specific coefficients with cluster-specific covariates:

$$\begin{aligned}\beta_{0j} &= \gamma_{00} + \gamma_{01}w_j + u_{0j}\\ \beta_{1j} &= \gamma_{10} + \gamma_{11}w_j + u_{1j}\end{aligned}$$

    - ◇ 'Intercepts and slopes as outcomes'

Reduced form model

- Substitute level-2 models into level-1 model:

$$\begin{aligned}y_{ij} &= \underbrace{\gamma_{00} + \gamma_{01}w_j + u_{0j}}_{\beta_{0j}} + \underbrace{(\gamma_{10} + \gamma_{11}w_j + u_{1j})}_{\beta_{1j}}x_{ij} + \epsilon_{ij}\\ &= \gamma_{00} + \gamma_{10}x_{ij} + \gamma_{01}w_j + \gamma_{11}w_jx_{ij} + u_{0j} + u_{1j}x_{ij} + \epsilon_{ij}\\ &\equiv \beta_1 + \beta_2x_{ij} + \beta_3w_j + \beta_4w_jx_{ij} + \zeta_{1j} + \zeta_{2j}x_{ij} + \epsilon_{ij}\end{aligned}$$

  - γ_{11} (or β_4) represents a **cross-level interaction** between w_j (level 2) and x_{ij} (level 1)

Example: Inner London Schools

- Inner London School data (65 schools)
  - Graduate Certificate of Secondary Education (GCSE) score (age 16) y_{ij}
  - London Reading Test (LRT) score before entering school (age 11) x_{ij}
  - GCSE and LRT standardized to mean=0, sd=10 (in larger sample)
- Model:

$$y_{ij} = \underbrace{(\beta_1 + \zeta_{1j})}_{\text{Intercept for school } j} + \underbrace{(\beta_2 + \zeta_{2j})}_{\text{Slope for school } j} x_{ij} + \epsilon_{ij}$$

  - With the usual assumptions

Maximum likelihood estimates for random intercept (RI) and random coefficient (RC) models

	RI Model		RC Model	
Parameter	Est	(SE)	Est	(SE)
Fixed part				
β_1	0.02	(0.40)	-0.12	(0.40)
β_2 [LRT]	0.56	(0.01)	0.56	(0.02)
Random part				
$\sqrt{\psi_{11}}$	3.04		3.01	
$\sqrt{\psi_{22}}$			0.12	
ρ_{21}			0.50	
$\sqrt{\theta}$	7.52		7.44	
Log-likelihood	-14024.80		-14004.61	

Test for zero slope variance

- H_0: $\psi_{22} = 0$ $(\Rightarrow \psi_{21} = 0)$; in other words $\zeta_{2j} = 0$ for all j
- If null hypothesis is true, likelihood ratio (or deviance) statistic G^2 usually has a χ^2 distribution with degrees of freedom equal to difference in number of parameters, here 2 $\Rightarrow$ p-value is < 0.001
- However, for variance component ψ_{22}, null hypothesis is on boundary of parameter space since $\psi_{22} \geq 0$
- Sampling distribution of G^2 under null hypothesis a 1:1 mixture of $\chi^2(2)$ and mass at 0
  $\Rightarrow$ divide p-value of conventional test by 2
  - p-value based on χ^2 distribution with d.f.$= 2$ is $p < 0.001$
  - Dividing by 2 gives same conclusion: random intercept model rejected in favor of random coefficient model

Predicted school-specific regression lines

$$\widehat{\mu}_{ij} \;=\; \widehat{\beta}_1 + \widehat{\beta}_2 x_{ij} + \widetilde{\zeta}_{1j} + \widetilde{\zeta}_{2j} x_{ij}$$

$\widetilde{\zeta}_{1j}$, $\widetilde{\zeta}_{2j}$ are **empirical Bayes** predictions

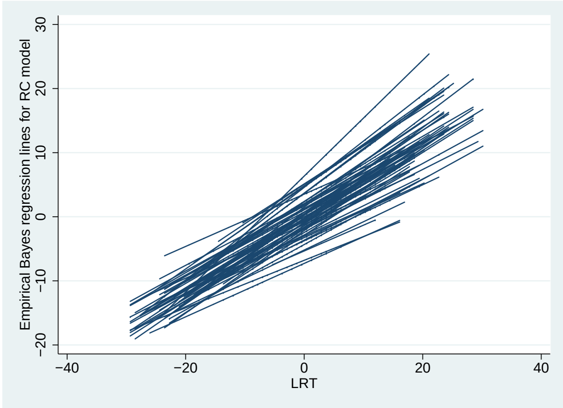
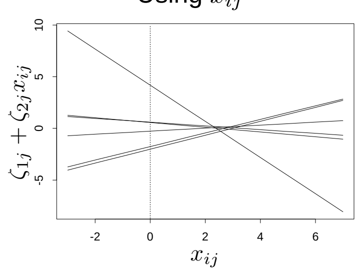


Illustration: Lack of invariance to translation and heteroscedasticity

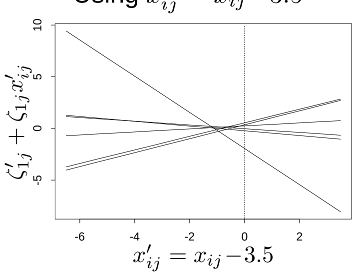
- Graphs of cluster-specific regression lines (with $\beta_1 = \beta_2 = 0$), illustrating effect of translation of x_{ij}:

Using x_{ij}



Large ψ_{11}, negative ψ_{21}

Using $x'_{ij} = x_{ij} - 3.5$



Small ψ_{11}, positive ψ_{21}

- Variance of $\zeta_{1j} + \zeta_{2j}x_{ij}$, and hence of total residual ξ_{ij} decreases with x_{ij} and increases again

Interpreting random part

- $\sqrt{\psi_{11}}$: Standard deviation of **intercepts**
  - Has same units (scale) as y_{ij} and β_1
    $\Rightarrow$ estimate rescaled when y_{ij} rescaled
    $\Rightarrow$ 95% of clusters expected to have intercepts in range $\beta_1 \pm 1.96\sqrt{\psi_{11}}$
  - Is standard deviation of vertical positions of cluster-specific regression lines were $x_{ij} = 0$
    $\Rightarrow$ estimate changes if x_{ij} translated (e.g., mean-centered)
- $\sqrt{\psi_{22}}$: Standard deviation of **slopes**
  - Has same units as β_2 (units of y_{ij} divided by units of x_{ij})
    $\Rightarrow$ cannot compare directly with $\sqrt{\psi_{11}}$
    $\Rightarrow$ estimate rescaled if either x_{ij} or y_{ij} are rescaled
    $\Rightarrow$ 95% of clusters expected to have slopes in range $\beta_2 \pm 1.96\sqrt{\psi_{22}}$

Interpreting random part (cont'd)

- ρ_{21}: Correlation between intercepts and slopes
  - Has no units ($-1 \leq \rho_{21} \leq 1$)
  - Is tendency for clusters with large intercepts to have large slopes $\Rightarrow$ estimate changes if x_{ij} translated
  - **Note:** Never set $\rho_{21} = 0$ (non-equivalent models if x_{ij} translated)
- $\sqrt{\theta}$: Standard deviation of level-1 residual ϵ_{ij}
  - Has same units as y_{ij}, β_1 and $\sqrt{\psi_{11}}$ $\Rightarrow$ estimate rescaled if y_{ij} rescaled
  - Is amount of scatter around cluster-specific regression lines
- **Note:** Since the scaling if y_{ij} and x_{ij} and the translation of x_{ij} matter for interpreting the random part, make meaningful choices
  - e.g., if x_{ij} is annual income in \$, express it as number of thousands above the average, i.e., generate transformed variable $z_{ij} = \frac{x_{ij}-\bar{x}_{..}}{1000}$

Interpreting random part for Inner London Schools

Parameter	Est	(SE)
β_1	−0.12	(0.40)
β_2 [LRT]	0.56	(0.02)
$\sqrt{\psi_{11}}$	3.01	
$\sqrt{\psi_{22}}$	0.12	
ρ_{21}	0.50	
$\sqrt{\theta}$	7.44	

- 95% of intercepts are in the range -6.0 to 5.8 ($-0.12 \pm 1.96 \times 3.01$)
- 95% of slopes are in the range 0.32 to 0.80 ($0.56 \pm 1.96 \times 0.12$)
- When LRT is at its mean, the SD of the school means is 3.01, less than half the within-school SD of 7.44

Warnings about random coefficient models

- Random slope rarely makes sense if there is no random intercept (just like interactions don't make sense without main effects)
- Random slope rarely makes sense without corresponding fixed slope (estimating variance, but constraining mean to zero)
- Models with several random slopes can be hard to estimate
  - With k random slopes (plus 1 random intercept) there are $(k+2)(k+1)/2+1$ parameters in random part e.g., $k=3$ gives 11 parameters in random part
  - Clusters may not provide much information on cluster-specific slopes or their variance if
    - Clusters are small
    - x_{ij} does not vary much within clusters, or varies only in a small number of clusters

Warnings about random coefficient models (cont'd)

- Variance-covariance matrix in random part may (try to) become non 'positive semi-definite' (e.g., negative variances, correlations greater than 1 or less than -1)
  If software does not allow this, get convergence problems
  - It may help to translate and rescale x_{ij}, or to simplify the model
- Overall message: Include random slopes only where strongly suggested by theory

III. Multilevel logistic regression

- Introduction to ordinary logistic regression
- Random intercept logistic regression
- Conditional and marginal relationships

Example: Attitudes to women's roles

- U.S. General Social Survey (GSS), independent samples in 1982 and 1994
- Responses to the question "Do you agree or disagree with this statement?"
  - "Women should take care of running their homes and leave running the country to men"

Year	Agree ($y_i = 1$)	Disagree ($y_i = 0$)	Total
1982 ($x_i = 0$)	122	223	345
1994 ($x_i = 1$)	268	1632	1900
Total	390	1855	2245

- x_i is a dummy variable for year being 1994

Probabilities, odds and odds ratio

- Probability $\equiv$ Proportion of people agreeing in population (Expected number of successes per trial)

$$0 \leq \text{Pr}(y_i = 1) \leq 1$$

  - Probability of agreeing in 1982 estimated as $\widehat{\text{Pr}}(y_i = 1|x_i = 0) = \frac{122}{345} = 0.354$
  - Probability of agreeing in 1994 estimated as $\widehat{\text{Pr}}(y_i = 1|x_i = 1) = \frac{268}{1900} = 0.141$
- Odds $\equiv$ Number of people agreeing per person disagreeing in population (Expected number of successes per failure)

$$0 \leq \text{Odds}(y_i = 1) \leq \infty$$

  - Odds of agreeing in 1982 estimated as $\widehat{\text{Odds}}(y_i = 1|x_i = 0) = \frac{122}{223} = 0.547$
  - Odds of agreeing in 1994 estimated as $\widehat{\text{Odds}}(y_i = 1|x_i = 1) = \frac{268}{1632} = 0.164$
- Odds ratio (OR) $= \dfrac{\text{Odds}(y_i=1|x_i=1)}{\text{Odds}(y_i=1|x_i=0)}$
  - Odds ratio is estimated as $\widehat{\text{OR}} = \frac{0.164}{0.547} = 0.300$

Logistic regression

- Logistic regression

$$\text{Pr}(y_i = 1|x_i) \;=\; \frac{\exp(\beta_1 + \beta_2 x_i)}{1 + \exp(\beta_1 + \beta_2 x_i)} \;=\; \frac{\text{Odds}(y_i = 1|x_i)}{1 + \text{Odds}(y_i = 1|x_i)}$$

- Log-odds

$$\log\left[\text{Odds}(y_i = 1|x_i)\right] \;\equiv\; \text{logit}[\text{Pr}(y_i = 1|x_i)] \;=\; \beta_1 + \beta_2 x_i$$

- Difference in log-odds for unit change in x_i (from a to $a+1$)

$$\log\left[\text{Odds}(y_i = 1|x_i = a+1)\right] - \log\left[\text{Odds}(y_i = 1|x_i = a)\right]$$
$$= [\beta_1 + \beta_2(a + 1)] - [\beta_1 + \beta_2 a] = \beta_2$$

- Odds ratio for unit change in x_i (from a to $a+1$)

$$\frac{\text{Odds}(y_i = 1|x_i = a+1)}{\text{Odds}(y_i = 1|x_i = a)} \;=\; \exp(\beta_2)$$

Example: *Logistic regression for attitudes to women's roles*

- Variables:
  - Dummy for year being 1994 (x_i)
  - Agreeing with statement (y_i)
- Maximum likelihood estimates:

	Est	(SE)	OR = exp(β)	(95% CI)
β_1	−0.60	(0.11)		
β_2 [1994]	−1.20	(0.13)	0.30	(0.23,0.39)

- 95% CI for OR is $\exp(\widehat{\beta}_2 - 1.96\text{SE}_{\widehat{\beta}_2}), \exp(\widehat{\beta}_2 + 1.96\text{SE}_{\widehat{\beta}_2})$
- Standard error for odds ratio not useful

Logistic regression as generalized linear model

- Linear predictor:

$$\nu_i \equiv \beta_1 + \beta_2 x_i$$

- Conditional expectation of y_i:

$$\mu_i \equiv \text{E}(y_i|x_i) = \text{E}(y_i|\nu_i)$$

  - For continuous responses, this is the population mean
  - For dichotomous responses (0,1), this is the probability $\Pr(y_{ij} = 1|\nu_i)$

Logistic regression as generalized linear model (cont'd)

- Link function $g()$ linking conditional expectation to linear predictor:

$$g(\mu_i) = \nu_i$$

  - Linear regression: $\mu_i = \nu_i$ (identity link)
  - Logistic regression: $\text{logit}(\mu_i) \equiv \log\left[\frac{\mu_i}{1-\mu_i}\right] = \nu_i$ (logit link)
  - Probit regression: $\Phi^{-1}(\mu_i) = \nu_i$ (probit link)
- Distribution of y_i given μ_i from exponential family:
  - Linear regression: Normal with mean μ_i and constant variance θ
  - Logit and probit: Bernoulli with probability μ_i (or binomial $B(1, \mu_i)$) – variance is $\mu_i(1 - \mu_i)$

Latent response y_i^*

- A continuous latent (unobserved) response y_i^* is often assumed to underlie the observed dichotomous response y_i
- Observed response $y_i = 1$ if latent response y_i^* exceeds threshold 0 and $y_i = 0$ otherwise
  - When asked to 'agree' or 'disagree' with a statement, respondent really agrees or disagrees to a certain extent (continuous scale), but is forced to choose one of the two responses
  - y_i^* can be viewed as the **propensity** to have the '1' response or the **utility difference** between alternatives '1' and '0'
    - ◇ e.g., the propensity (or inclination) to have a child vaccinated has to exceed some limit for the parent to have the child vaccinated
  - Death results when some continuous frailty exceeds a limit, or when exposure to some hazardous materials exceeds a limit

Latent response y_i^* (cont'd)

- Idea of latent response introduced by Pearson in 1901
- Yule remarked in 1912:

  > ...all those who have died of smallpox are equally dead: no one is more dead or less dead than another, and the dead are quite distinct from the survivors

- Pearson and Heron responded in 1913:

  > ...if Mr Yule's views are accepted, irreperable damage will be done to the growth of modern statistical theory

- Latent response models useful even if we do not believe in y_i^*

Latent response formulation

- Latent response model is a linear regression model

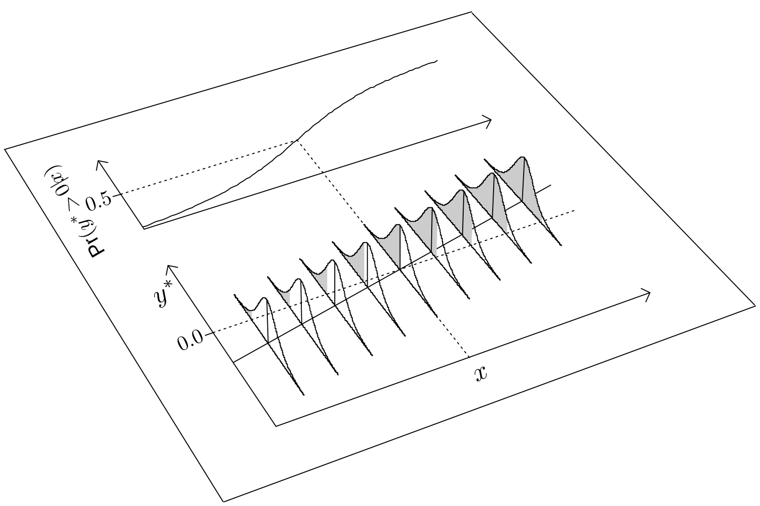
$$y_i^* \;=\; \beta_1 + \beta_2 x_i + \epsilon_i$$

- Observed response results as follows (deterministic):

$$y_i \;=\; \begin{cases} 1 & \text{if } y_i^* > 0 \\ 0 & \text{otherwise} \end{cases}$$

- Logistic regression model:
  - ϵ_i has a standard logistic distribution (variance $\pi^2/3$)
- Probit model:
  - ϵ_i has a standard normal distribution (variance 1)

Latent response formulation of logistic regression



Equivalence of generalized linear model and latent response formulation

- Can calculate the probability that $y_i = 1$ using latent resonse formulation:

$$\begin{aligned} \Pr(y_i = 1|x_i) &= \Pr(y_i^* > 0|x_i) = \Pr(\beta_1+\beta_2 x_i+\epsilon_i > 0|x_i) \\ &= \Pr(-\epsilon_i \le \beta_1+\beta_2 x_i|x_i) \\ &= \Pr(\epsilon_i \le \beta_1+\beta_2 x_i|x_i), \quad \text{the CDF of } \epsilon_i \end{aligned}$$

  - Logistic CDF of ϵ_i results in logistic regression:

$$\Pr(y_i = 1|x_i) = \frac{\exp(\beta_1+\beta_2 x_i)}{1+\exp(\beta_1+\beta_2 x_i)}$$

  - Standard normal CDF $\Phi(\cdot)$ of ϵ_i results in probit regression:

$$\Pr(y_i = 1|x_i) = \Phi(\beta_1+\beta_2 x_i)$$

Example: Toenail infection

- 337 patients with toenail infection randomized to receive terbinafine or itraconazole
- Assessments scheduled at 7 visits; weeks 0, 4, 8, 12, 24, 36, and 48
- Variables:
  - Onycholysis (separation of nail plate from nail bed) y_{ij} (0:none or mild, 1:moderate or severe)
  - Treatment group (0:itraconazole, 1:terbinafine) x_{2j}
  - Exact timing of visit in months x_{3ij}
  - Visit number (1,2,. . .,7)

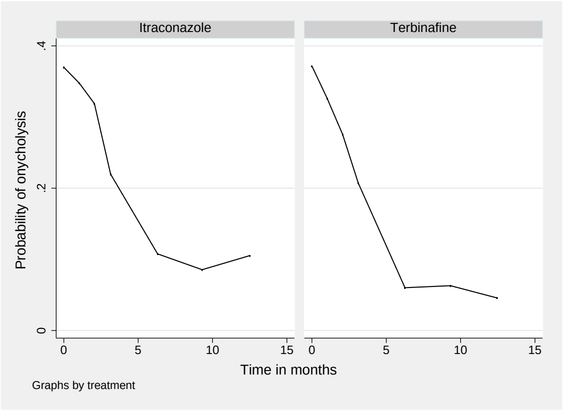
Exploring missingness patterns

Freq.	Percent	Cum.	Pattern
224	76.19	76.19	1111111
21	7.14	83.33	11111.1
10	3.40	86.73	1111.11
6	2.04	88.78	111....
5	1.70	90.48	1......
5	1.70	92.18	11111..
4	1.36	93.54	1111...
3	1.02	94.56	11.....
3	1.02	95.58	111.111
13	4.42	100.00	(other patterns)
294	100.00		XXXXXXX

- 224 patients have complete data, 21 patients missed visit 6, 10 patients missed visit 5, 6 patients dropped out after visit 3, etc.

Plot of raw estimates of marginal probabilities

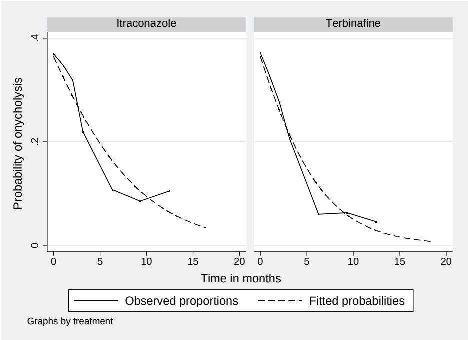
- Proportion with onycholysis at each occasion, versus average time at each visit since randomization



Logistic regression model for marginal probabilities

$$\text{logit}[\Pr(y_{ij}=1|x_{2j},x_{3ij})] \;=\; \beta_1+\beta_2 x_{2j}+\beta_3 x_{3ij}+\beta_4 x_{2j}x_{3ij}$$

- Regression coefficients and odds-ratios have **marginal** or **population averaged** interpretations, comparing prevalences for different population strata
- Plot of predicted probabilities together with raw estimates:



Random intercept logistic regression

- Ordinary logistic regression fits marginal proportions quite well
- However, unobserved heterogeneity between subjects and dependence within subjects are ignored
- Include a random intercept ζ_j:

$$\text{logit}[\Pr(y_{ij}=1|x_{2j},x_{3ij},\zeta_j)] \;=\; \beta_1+\beta_2x_{2j}+\beta_3x_{3ij}+\beta_4x_{2j}x_{3ij}+\zeta_j$$

or

$$y^*_{ij} \;=\; \beta_1+\beta_2x_{2j}+\beta_3x_{3ij}+\beta_4x_{2j}x_{3ij}+\zeta_j+\epsilon_{ij}$$

  - ζ_j enters in same manner as observed covariates
  - Assume $\zeta_j \sim \text{N}(0,\psi)$, independent of x_{2j}, x_{3ij}, and of ϵ_{ij} in latent response formulation (ϵ_{ij} has standard logistic distribution)
- Regression coefficients and odds-ratios have **conditional** or **cluster-specific** interpretations, comparing probabilities holding ζ_j constant

Estimation: Maximum likelihood

- Estimation for categorical responses difficult because marginal (or integrated) likelihood involves integrals that do not have closed form
- Numerical integration
  - Gauss-Hermite (ordinary) quadrature used in `MIXOR`/`MIXNO` (two-level only) and `aML`
  - Adaptive quadrature superior, particularly for large clusters and large variances. Available in SAS: `GLIMMIX` and Stata: `gllamm`, `xtmelogit`, etc., S-PLUS: `glme`, `Mplus`
- Monte Carlo integration
  - Simulated maximum likelihood in `nlogit`, Stata: `mixlogit`
  - Monte Carlo EM - no software?
- Markov chain Monte Carlo (MCMC) with vague priors approximates maximum likelihood and available in `MLwiN` and `WinBUGS`

Estimation: Approximate methods

- Penalized Quasilikelihood (PQL)
  - Two versions: First and second order (PQL-1,PQL-2), the latter being better
    - ◇ PQL-1 in `MLwiN`, `HLM` and SAS: `GLIMMIX`
    - ◇ PQL-2 in `MLwiN`
    - ◇ Even PQL-2 produces biased estimates for small clusters and large level-2 variances
- Laplace: R: `lmer` and Stata: `xtmelogit`
- Sixth order Laplace in `HLM`
- H-likelihood in `Genstat`
- Methods do not provide a likelihood

Maximum likelihood estimates

	Marginal effects		Conditional effects	
	Ordinary logistic		Random intercept logistic	
Parameter	OR	(95% CI)	OR	(95% CI)
Fixed part				
$\exp(\beta_2)$ [`treatment`]	1.00	(0.74, 1.36)	0.85	(0.27, 2.65)
$\exp(\beta_3)$ [`month`]	0.84	(0.81, 0.88)	0.68	(0.62, 0.74)
$\exp(\beta_4)$ [`trt_month`]	0.93	(0.87, 1.01)	0.87	(0.76, 1.00)
Random part				
ψ			16.08	
Log-likelihood	−908.01		−625.39	

Intraclass correlation of latent responses

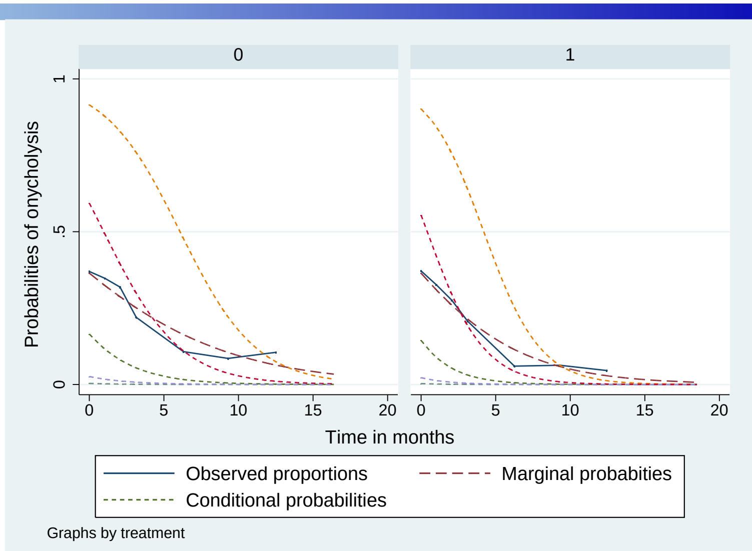
- Correlation between observed responses in the same cluster, given the covariates
$$\text{Cor}(y_{ij}, y_{i'j} | x_{2j}, x_{3ij}, x_{3i'j})$$
is a function of x_{2j}, x_{3ij}, and $x_{3i'j}$
- Therefore, report correlation between **latent responses** in same cluster, given covariates
$$\text{Cor}(y^*_{ij}, y^*_{i'j} | x_{2j}, x_{3ij}, x_{3i'j}) \;=\; \frac{\psi}{\psi + \pi^2/3}$$
  - Estimated intraclass correlation for toenail data:
$$\frac{\widehat{\psi}}{\widehat{\psi} + \pi^2/3} = 0.83$$

Marginal and conditional relationships

- Note that marginal OR closer to 1 than conditional OR
- Marginal probabilities from random intercept model

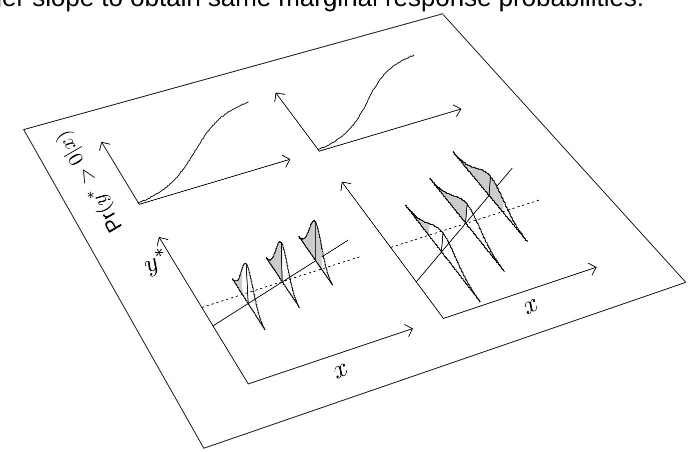
$$\begin{aligned}\text{Pr}(y_{ij} &= 1 | x_{2j}, x_{3ij}) \\ &= \int \text{Pr}(y_{ij} = 1 | x_{2j}, x_{3ij}, \zeta_j) g(\zeta_j; 0, \widehat{\psi})\, \mathrm{d}\zeta_j \\ &= \int \frac{\exp(\widehat{\beta}_1 + \widehat{\beta}_2 x_{2j} + \widehat{\beta}_3 x_{3ij} + \widehat{\beta}_4 x_{2j} x_{3ij} + \zeta_j)}{1 + \exp(\widehat{\beta}_1 + \widehat{\beta}_2 x_{2j} + \widehat{\beta}_3 x_{3ij} + \widehat{\beta}_4 x_{2j} x_{3ij} + \zeta_j)}\, g(\zeta_j; 0, \widehat{\psi})\, \mathrm{d}\zeta_j\end{aligned}$$

Marginal and conditional relationships (cont'd)



Reason for difference between conditional and marginal effects: Using latent response formulation

- Larger residual standard deviation, $\text{Var}(\zeta_j + \epsilon_{ij}) > \text{Var}(\epsilon_{ij})$, requires larger slope to obtain same marginal response probabilities:



Conditional and marginal effects for probit random intercept model

- Probit random intercept model: $y_{ij}^* = \beta_1 + \beta_2 x_{ij} + \underbrace{\zeta_j + \epsilon_{ij}}_{\xi_{ij}}$

  $\zeta_j \sim \mathrm{N}(0,\psi)$, $\epsilon_{ij} \sim \mathrm{N}(0,1) \quad \Rightarrow \quad \xi_{ij} = \zeta_j + \epsilon_{ij} \sim \mathrm{N}(0, \psi+1)$
- Conditional probability

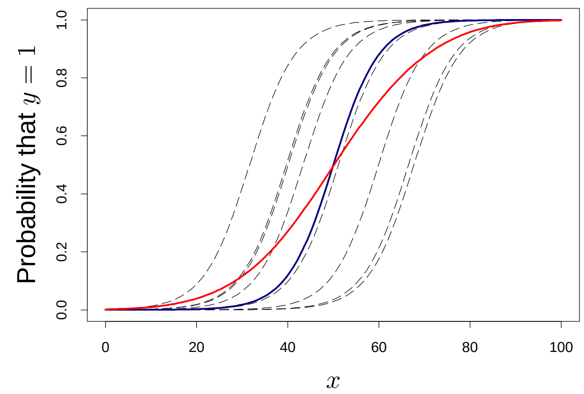
$$\Pr(y_{ij}=1|x_{ij},\zeta_j) = \Phi(\beta_1 + \beta_2 x_{ij} + \zeta_j)$$

- Marginal probability

$$\begin{aligned}
\Pr(y_{ij}=1|x_{ij}) &= \Pr(y_{ij}^*>0|x_{ij}) = \Pr(\beta_1+\beta_2 x_{ij}+\xi_{ij}>0|x_{ij}) \\
&= \Pr(-\xi_{ij} \le \beta_1+\beta_2 x_{ij}|x_{ij}) = \Pr(\xi_{ij} \le \beta_1+\beta_2 x_{ij}|x_{ij}) \\
&= \Pr(\frac{\xi_{ij}}{\sqrt{\psi+1}} \le \frac{\beta_1+\beta_2 x_{ij}}{\sqrt{\psi+1}}|x_{ij}) \\
&= \Phi(\frac{\beta_1+\beta_2 x_{ij}}{\sqrt{\psi+1}})
\end{aligned}$$

- Marginal effect **attenuated** or closer to zero: $|\beta_2/\sqrt{\psi+1}| \le |\beta_2|$

Illustration: Conditional versus marginal relationship



- - - - - cluster-specific (random sample)
——— median
——— marginal or population-averaged

Interpretation of regression parameter for within-cluster covariate

- **Conditional effects** or **subject-specific effects**:
  - Subject-specific odds ratios, e.g. for [month] $a+1$ versus a when [treatment] = 0

$$\exp(\beta_3^{\mathrm{C}}) = \frac{\Pr(y_{ij}=1|x_{ij}=a+1,x_j=0,\zeta_j)}{\Pr(y_{ij}=0|x_{ij}=a+1,x_j=0,\zeta_j)} \Big/ \frac{\Pr(y_{ij}=1|x_{ij}=a,x_j=0,\zeta_j)}{\Pr(y_{ij}=0|x_{ij}=a,x_j=0,\zeta_j)}$$

    - ◇ Comparing odds for particular subject j (conditional on ζ_j)
- **Marginal effects** or **population-averaged effects**:
  - Marginal odds ratios

$$\exp(\beta_3^{\mathrm{M}}) = \frac{\Pr(y_{ij}=1|x_{ij}=a+1,x_j=0)}{\Pr(y_{ij}=0|x_{ij}=a+1,x_j=0)} \Big/ \frac{\Pr(y_{ij}=1|x_{ij}=a,x_j=0)}{\Pr(y_{ij}=0|x_{ij}=a,x_j=0)}$$

    - ◇ Comparing odds for population strata (not conditional on ζ_j)

Interpretation of regression parameter for between-cluster covariate

- **Conditional effects** or **subject-specific effects**:
  - Subject-specific odds ratios, e.g. for [treatment] 1 versus 0 when [month] = 1

$$\exp(\beta_2^{\mathrm{C}}+\beta_4^{\mathrm{C}}) = \frac{\Pr(y_{ij}=1|x_j=1,x_{ij}=1,\zeta_j)}{\Pr(y_{ij}=0|x_j=1,x_{ij}=1,\zeta_j)} \Big/ \frac{\Pr(y_{ij}=1|x_j=0,x_{ij}=1,\zeta_j)}{\Pr(y_{ij}=0|x_j=0,x_{ij}=1,\zeta_j)}$$

    - ◇ Comparing **counterfactual** odds for particular subject j
- **Marginal effects** or **population-averaged effects**:
  - Marginal odds ratios

$$\exp(\beta_2^{\mathrm{M}}+\beta_4^{\mathrm{M}}) = \frac{\Pr(y_{ij}=1|x_j=1,x_{ij}=1)}{\Pr(y_{ij}=0|x_j=1,x_{ij}=1)} \Big/ \frac{\Pr(y_{ij}=1|x_j=0,x_{ij}=1)}{\Pr(y_{ij}=0|x_j=0,x_{ij}=1)}$$

    - ◇ Comparing odds for population strata

Pros and cons of conditional and marginal effects

- Marginal effects
  - Of interest for policy, e.g. public health
  - Not invariant across populations (depend on ψ)
- Conditional effects
  - Of interest for individuals, e.g. patients
  - More useful for investigating causal processes
  - More invariant across populations

Two-stage formulation

- Raudenbush and Bryk -style notation for two-level logistic models
  - Level-1 model

$$\begin{aligned}\varphi_{ij} &\equiv \text{Pr}(y_{ij}=1|\nu_{ij}) = \text{E}(y_{ij}|\nu_{ij})\\ y_{ij}|\varphi_{ij} &\sim \text{Binomial}(1,\varphi_{ij}) \equiv \text{Bernoulli}(\varphi_{ij}) \quad \text{('sampling model')}\\ \text{logit}(\varphi_{ij}) &= \beta_{0j}+\beta_{1j}x_{1ij}+\beta_{2j}x_{2ij} \equiv \nu_{ij} \quad \text{('structural model')}\end{aligned}$$

  - Level-2 models

$$\begin{aligned}\beta_{0j} &= \gamma_{00}+\gamma_{01}w_{1j}+\gamma_{02}w_{2j}+u_{0j}\\ \beta_{1j} &= \gamma_{10}+\gamma_{11}w_{1j}+\gamma_{12}w_{2j}+u_{1j}\\ \beta_{2j} &= \gamma_{20}\end{aligned}$$

where $(u_{0j},u_{1j})' \sim \text{N}(\mathbf{0},\boldsymbol{\tau}), \quad \boldsymbol{\tau} = \begin{bmatrix}\tau_{00} & \tau_{01}\\ \tau_{10} & \tau_{11}\end{bmatrix}$

IV. Longitudinal data and alternatives to multilevel modeling

- Longitudinal data
- Example: Wage and experience
- Linear growth curve models
- Nonlinear growth
- Example: Children's growth
- Fixed effects approach
- Marginal versus multilevel approach
- Autoregressive approaches
- Dropout and missing data
- Three-level models
- Example: Sustaining effects study

Longitudinal studies

- Panel surveys
  - All subjects followed up at the same panel waves $\Longrightarrow$ balanced data
- Cohort studies (as defined in epidemiology)
  - Cohort is any group of individuals, often same age ("birth cohort")
  - Generally, not followed up at the same time $\Longrightarrow$ unbalanced data
  - Intervention studies and clinical trials are special cases
- Other related types of studies (not discussed here)
  - Time-series for a single unit over time
  - Longitudinal information collected retrospectively $\Longrightarrow$ Recall bias
  - Survival, durations, or time-to event data

Longitudinal data

- Variables for subject j at occasion (e.g., panel wave) i
  - Response variable (time-varying) y_{ij}
  - Explanatory variable
    - ◇ Subject-specific (time-constant) x_j, e.g. gender
    - ◇ Occasion-specific x_i, e.g. calendar time
    - ◇ Subject and occasion-specific (time-varying) x_{ij}, e.g. marital status
- Longitudinal data are balanced if occasions for each subject correspond to same time points
  - Can treat responses at different occasions as different variables & use multivariate methods (e.g., Structural equation modeling)
  - Can model means and covariances more freely
- Intermittent missing data and dropout or attrition are common

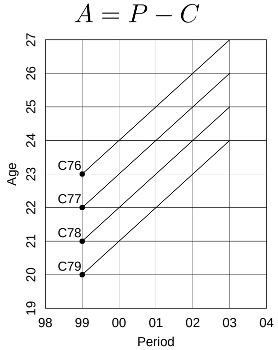
Longitudinal data (cont'd)

Subject j	Occ. i	Born x_{1j}	Age x_{2ij}	Year x_{3i}	Gender x_{4j}	Married x_{5ij}	Happiness y_{ij}
1	1	1960	35	1995	Male	1	1
1	2	1960	40	2000	Male	0	6
1	3	1960	45	2005	Male	1	3
2	1	1980	15	1995	Female	0	5
2	2	1980	20	2000	Female	0	4
2	3	1980	25	2005	Female	1	1
		Cohort	Age	Period			

Three time scales

- Age A: Time since birth
- Period P: Current calendar time (time since birth of Christ)
- Cohort C: Calendar time at time of birth

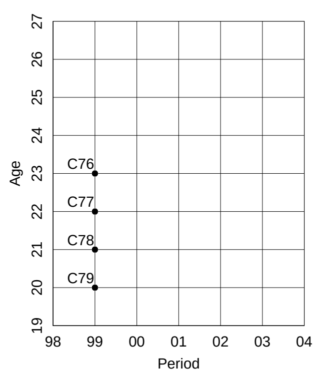
$$A = P - C$$



- Alternative age-like timescale: Time since subject-specific event such as surgery (then cohort becomes time of surgery)

Age-Period-Cohort effects: Cross-sectional study

- One period P
  $\Longrightarrow$ cannot estimate effect of period
- Different ages A_j, $\quad A_j = P - C_j$
  $\Longrightarrow$ age and cohort effects confounded



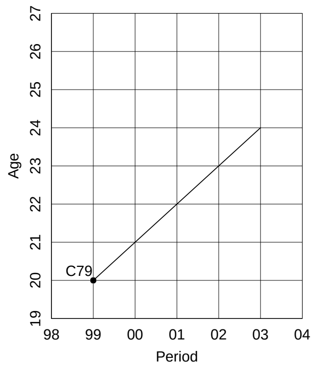
e.g., explanations for older people being more conservative:

(1) later stage in life A_j

(2) born longer ago (into a different 'era') C_j

Age-Period-Cohort effects: Longitudinal study, one cohort

- One cohort C
  $\Longrightarrow$ cannot estimate effect of cohort
- Different periods P_i and ages A_i, $\quad A_i = P_i - C$
  $\Longrightarrow$ period and age effects confounded



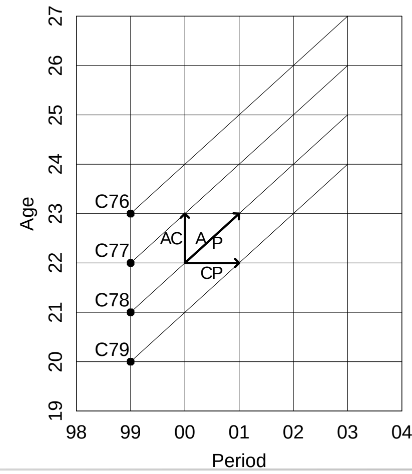
e.g., explanations for salary increases:

(1) more experience A_i

(2) inflation P_i

Age-Period-Cohort effects: Longitudinal study, several cohorts

- Several cohorts C_j, different periods P_i and ages A_{ij}, $\quad A_{ij} = P_i - C_j$
  $\Longrightarrow$ can estimate effects of two time scales, but confounded with third



Pick time scales believed to be most important

$\Rightarrow$ e.g., Conservatism depends on age and cohort (ignore period)

$\Rightarrow$ e.g., Salary depends on age and period (ignore cohort)

Other terms for design:
Accelerated longitudinal
Cohort-sequential

Example: Wage and experience

- US National Longitudinal Survey of Youth 1979 (NLSY79)
  - Representative sample of non-institutionalized, civilian U.S. youth
  - 6,111 men and women, aged 14-21 in Dec 31, 1978
  - Subsample of 545 considered here:
    - ◇ Full-time working males who completed schooling by 1980
    - ◇ Complete data for 1980-1987
  - Variables:
    - ◇ Subject identifier j
    - ◇ Log hourly wage lny_{ij}
    - ◇ Education (number of years) E_j
    - ◇ Labor market experience (in years) L_{ij}
    - ◇ Period (1980-1987) P_i
- How does log hourly wage depend on labor market experience L_{ij} and period P_i, controlling for education E_j?

Time scales in NLSY79

- Note that there are at least 5 time-scales:
$$A_{ij} \;=\; 6 + E_j + L_{ij} \;=\; P_i - C_j$$
  - A_{ij} determined by (and thus confounded with) E_j and L_{ij}
  - C_j determined by (and thus confounded with) P_i, L_{ij} and E_j
- Random intercept model: ln$y_{ij} = \beta_1 + \beta_2 L_{ij} + \beta_3 P_i + \beta_4 E_j + \zeta_j + \epsilon_{ij}$

	Est	(SE)	exp(Est)
Fixed Part:			
β_1	−52.99	(23.23)	
β_2 [L_{ij}]	0.04	(0.01)	1.04
β_3 [P_i]	0.03	(0.01)	1.03
β_4 [E_j]	0.10	(0.01)	1.11
Random Part:			
$\sqrt{\psi}$	0.34		
$\sqrt{\theta}$	0.35		

Linear growth curve models

- Appropriate for balanced or unbalanced data
- In R&B two-stage formulation, linear growth curve model (level 1):

$$y_{ij} = \beta_{0j} + \beta_{1j} t_{ij} + r_{ij}$$

  - Each subject grows linearly, starting at level β_{0j} (when $t_{ij} = 0$) and growing at a rate of β_{1j} per unit of time (e.g., year)
  - Define level-2 models to explain variability in initial status β_{0j} and growth rate β_{1j} using subject-specific covariate x_j

$$\begin{aligned} \beta_{0j} &= \gamma_{00} + \gamma_{01} x_j + u_{0j} \\ \beta_{1j} &= \gamma_{10} + \gamma_{11} x_j + u_{1j} \end{aligned}$$

- Reduced form formulation:

$$y_{ij} = \beta_1 + \beta_2 x_j + \beta_3 t_{ij} + \beta_4 x_j t_{ij} + \zeta_{1j} + \zeta_{2j} t_{ij} + \epsilon_{ij}$$

Nonlinear growth: Polynomial model

- Change fixed part of model to allow for nonlinear growth
- Saturated model for balanced data: use dummy variables for each time point except first
- Polynomial model

$$y_{ij} = \beta_{1j} + \beta_{2j} t_{ij} + \beta_{3j} t_{ij}^2 + \cdots + \beta_{p+1,j} t_{ij}^p + \cdots$$

  - Smooth function, but can get weird artifacts
  - Order of polynomial p determines flexibility – number of extrema is $p - 1$
  - Not all coefficients must be random
  - For balanced data, cannot have more coefficients than time points

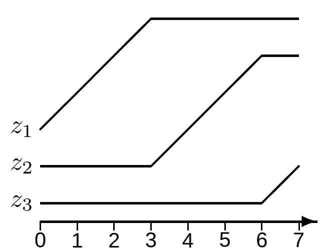
Nonlinear growth: Piecewise linear model

- Model, with linear spline basis functions z_{kij}

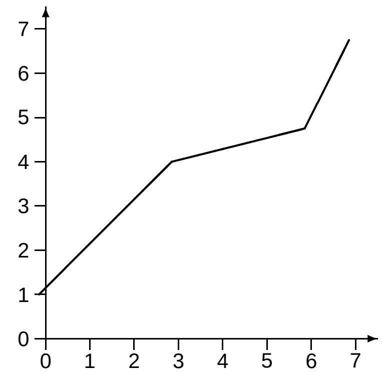
$$y_{ij} = \beta_1 + \beta_2 z_{1ij} + \cdots + \beta_{K+1} z_{Kij} + \cdots$$

- Example: $t_{ij} = i$, $i = 0, \ldots, 7$, and spline knots at $\tau_1 = 3$, $\tau_2 = 6$

t_{ij}	Interval	z_{1ij}	z_{2ij}	z_{3ij}
0	1	0	0	0
1	1	1	0	0
2	1	2	0	0
3	1	3	0	0
4	2	3	1	0
5	2	3	2	0
6	2	3	3	0
7	3	3	3	1



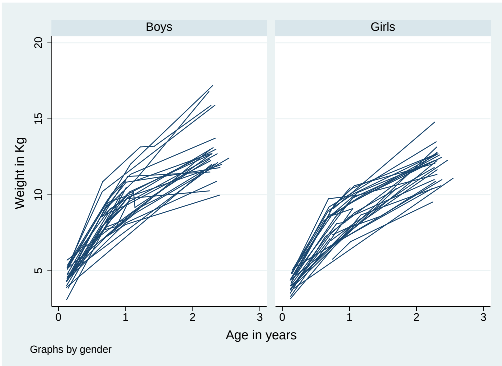
Nonlinear growth: Piecewise linear model (cont'd)



$1 + z_{1ij} + 0.25 z_{2ij} + 2 z_{3ij}$

Example: Children's growth

- Asian children in Britain weighed from age 6 weeks to 27 months:
  - Weight in Kg
  - Age in years
  - Gender (1:boy, 2:girl)
- Plot of observed trajectories



Maximum likelihood estimates (fixed part)

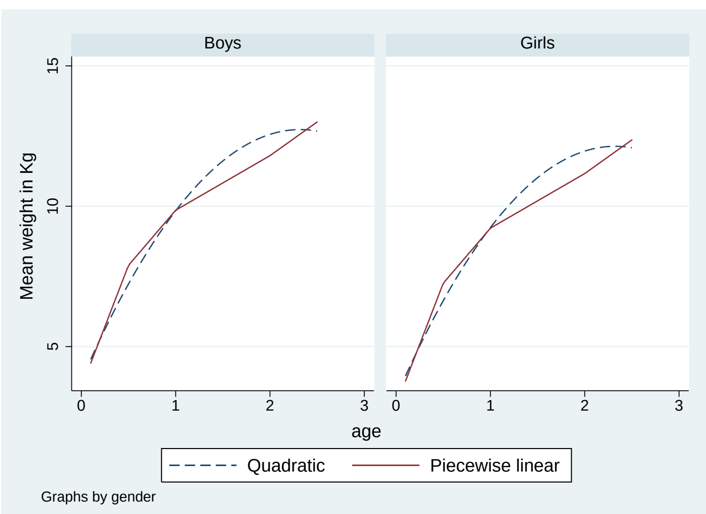
- Polynomial (quadratic)

	Est	(SE)
β_1	3.75	(0.17)
β_2 [girl]	−0.54	(0.21)
β_3 [age]	7.81	(0.25)
β_4 [agesq]	−1.66	(0.09)

- Piecewise linear (4 pieces), knots at 0.5, 1, 2

	Est	(SE)
β_1	3.34	(0.18)
β_2 [girl]	−0.64	(0.20)
β_3 [age1]	8.71	(0.45)
β_4 [age2]	3.93	(0.40)
β_5 [age3]	1.95	(0.70)
β_6 [age4]	2.40	(0.38)

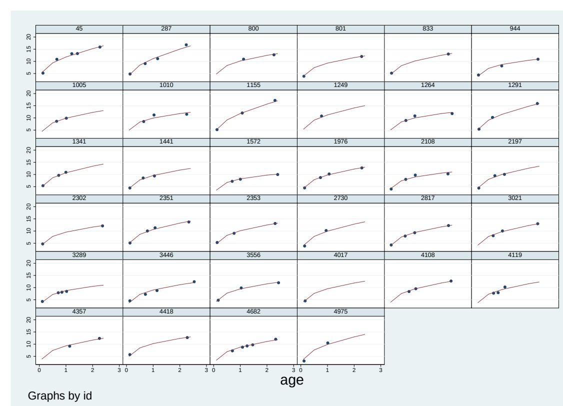
Estimated population averaged trajectories



Estimated subject-specific trajectories

- 'Trellis graph' of estimated cluster-specific trajectories (for boys)

$$\widehat{\mu}_{ij} = \widehat{\beta}_1 + \widehat{\beta}_2 \texttt{girl}_j + \widehat{\beta}_3 \texttt{age1}_{ij} + \widehat{\beta}_4 \texttt{age2}_{ij} + \widehat{\beta}_5 \texttt{age3}_{ij} + \widehat{\beta}_6 \texttt{age4}_{ij} + \widetilde{\zeta}_{1j} + \widetilde{\zeta}_{2j} \texttt{age}_{ij}$$



Fixed-effects models

- Avoid endogeneity or subject-level confounding by using fixed-effects models to estimate within-effects
  - Subjects truly act as their own controls
- For linear and log-linear models
  - Include dummy variables, or use conditional maximum likelihood (in linear case by sweeping out the subject mean)
- For logistic regression models:
  - Cannot include dummy variables for subjects due to incidental parameter problem, leading to inconsistent estimates of within-effects
  - Can use conditional logistic regression (conditional maximum likelihood, conditioning on sum of responses for subjects)

Disadvantages of fixed-effects models

- Cannot include subject-level covariates such as gender
- Inefficient if covariate(s) and/or response variable vary mostly between subjects
- Allows only for subject-specific intercepts (not slopes) for logistic regression
- Not possible for probit or ordinal models
- No direct information on unobserved heterogeneity
- Cannot make predictions for units in new clusters

Reminder: Marginal versus conditional

$$y_{ij} = \beta_1 + \beta_2 t_{ij} + \underbrace{\zeta_{1j} + \zeta_{2j} t_{ij} + \epsilon_{ij}}_{\xi_{ij}}$$

- Can consider conditional, or subject-specific expectation, given random effects ζ_{1j}, ζ_{2j}:

$$\text{E}(y_{ij}|t_{ij}, \zeta_{1j}, \zeta_{2j}) = \beta_1 + \beta_2 t_{ij} + \zeta_{1j} + \zeta_{2j} t_{ij}$$

- Conditional variance is θ and conditional covariances are zero
- Can consider marginal mean, variances and covariances

$$\text{E}(y_{ij}|t_{ij}) = \beta_1 + \beta_2 t_{ij}$$

$$\text{Var}(y_{ij}|t_{ij}) = \text{Var}(\xi_{ij}|t_{ij}) \;=\; \psi_{11} + 2\psi_{21} t_{ij} + \psi_{22} t_{ij}^2 + \theta$$

$$\text{Cov}(y_{ij}, y_{i'j}|t_{ij}, t_{i'j}) = \text{Var}(\xi_{ij}, \xi_{i'j}|t_{ij}, t_{i'j}) \;=\; \psi_{11} + \psi_{21}(t_{ij} + t_{i'j}) + \psi_{22} t_{ij} t_{i'j}$$

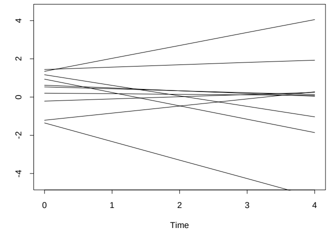
Marginal covariance matrix for linear growth curve model (5 occasions, $t = 0, 1, 2, 3, 4$)

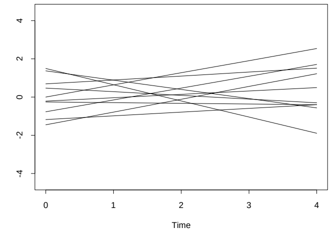
Random part

$$\boldsymbol{\Psi} = \begin{bmatrix} 1.00 & 0.10 \\ 0.10 & 0.25 \end{bmatrix} \qquad \theta = 0.5$$

$$\boldsymbol{\Psi} = \begin{bmatrix} 1.00 & -0.40 \\ -0.40 & 0.25 \end{bmatrix} \qquad \theta = 0.5$$

Subject-specific trajectories (β_1=β_2=0)





Residual variances

$$\begin{bmatrix} 1.50 & 1.95 & 2.90 & 4.35 & 6.30 \end{bmatrix}$$

$$\begin{bmatrix} 1.50 & 0.95 & 0.90 & 1.35 & 2.30 \end{bmatrix}$$

Residual correlations

$$\begin{bmatrix} 1.00 & & & & \\ 0.63 & 1.00 & & & \\ 0.58 & 0.76 & 1.00 & & \\ 0.51 & 0.74 & 0.84 & 1.00 & \\ 0.46 & 0.71 & 0.84 & 0.90 & 1.00 \end{bmatrix}$$

$$\begin{bmatrix} 1.00 & & & & \\ 0.50 & 1.00 & & & \\ 0.17 & 0.32 & 1.00 & & \\ -0.14 & 0.13 & 0.45 & 1.00 & \\ -0.32 & 0.00 & 0.42 & 0.68 & 1.00 \end{bmatrix}$$

Population-averaged or marginal approach to longitudinal data

- Instead of modeling individual trajectories (multilevel approach), model mean response and covariance matrix of (total) residual directly as functions of time ('Marginal model')
- Popular residual covariance structures
  - **Compound symmetric** or **exchangeable**: All variances equal and all covariances (and hence correlations) equal
    - If correlation is positive, random intercept model with variance $\psi + \theta$ and covariance ψ
  - **Autoregressive**: Correlations fall off as time lag increases
    - Popular special case: first order autoregressive, AR(1)

$$\text{Cor}(\xi_{ij}, \xi_{i'j}) = \alpha^{|t_i - t_{i'}|}$$

  - **Unstructured**: Each variance and covariance is freely estimated
    - Seems best, but inefficient (imprecise) if many time points

Illustration with three time-points

- Maximum likelihood estimates of residual variances and correlation matrices (alcohol use data, not discussed here)

Unstructured	AR(1)	Exchangeable	Growth curve model
$\begin{bmatrix} 0.52 & 0.77 & 1.11 \end{bmatrix}$	$\begin{bmatrix} 0.80 & 0.80 & 0.80 \end{bmatrix}$	$\begin{bmatrix} 0.80 & 0.80 & 0.80 \end{bmatrix}$	$\begin{bmatrix} 0.60 & 0.72 & 1.15 \end{bmatrix}$
$\begin{bmatrix} 1.00 & & \\ 0.44 & 1.00 & \\ 0.26 & 0.53 & 1.00 \end{bmatrix}$	$\begin{bmatrix} 1.00 & & \\ 0.49 & 1.00 & \\ 0.24 & 0.49 & 1.00 \end{bmatrix}$	$\begin{bmatrix} 1.00 & & \\ 0.40 & 1.00 & \\ 0.40 & 0.40 & 1.00 \end{bmatrix}$	$\begin{bmatrix} 1.00 & & \\ 0.38 & 1.00 & \\ 0.28 & 0.57 & 1.00 \end{bmatrix}$
-293.0 (6)	-299.3 (2)	-303.2 (2)	-294.3 (4)

Generalized estimating equations (GEE)

- Covariance structures for residuals are natural in linear models, giving multivariate regression models that can be estimated by maximum likelihood (ML)
- For binary and other non-continuous outcomes, can pretend that this is still possible
  - Specify structures for means and covariances $\Rightarrow$ Quasilikelihood
  - Use **estimating equations**, like "score equations" for ML
  - Estimation alternates between estimation of
    1. Regression coefficients: Generalized least squares for linearized model
    2. Covariance parameters: Moment estimators based on residuals
  - Not a true statistical model

Advantages of multilevel over marginal approach

- Multilevel model 'explains' covariance structure in terms of variability in intercepts and slopes
  - In marginal model, tempting to specify meaningless structures, such as constant variance over time in growth model (as in standard GEE)
- Multilevel model provides conditional or subject-specific interpretation $\Rightarrow$ stable across populations differing in between-subjects variability
- Multilevel model is proper statistical model for any response type
  - Can conceptualize as data-generating mechanism
  - Can simulate from the model
  - Can derive marginal relationships
  - Can make predictions and perform diagnostics based on predictions
  - Can perform likelihood ratio tests

Advantages of marginal over multilevel approach

- Permits more flexible covariance structures, e.g., negative intraclass correlation
- For non-continuous responses:
  - Marginal approach has marginal or population-averaged interpretation
    - Descriptive and easy to interpret; less likely to get extreme coefficients
  - Marginal approach via GEE gives consistent estimates of regression coefficients even if covariance structure misspecified (assuming correct fixed part)
  - GEE is computationally efficient (e.g., no numerical integration)

Models with autoregressive (AR) responses

- AR(1) model for response, conditioning on previous response $y_{i-1,j}$:

$$y_{ij} \;=\; \beta_1 + \gamma y_{i-1,j} + \beta_2 x_{ij} + \epsilon_{ij}, \qquad |\gamma| < 1$$

- Also called dynamic, lagged response or transition models
- Should be used only if effect γ of lagged response is of substantive interest ('state dependence' for binary responses)
- Advantage:
  - Easy to implement in linear as well as non-linear models
- Disadvantages:
  - Only sensible for equally spaced time-points
  - Discarding data: Lags missing for first occasion, missing responses and subsequent responses discarded
  - Initial conditions problem if true model contains subject-specific effects ζ_j

Models with autoregressive (AR) residuals

- AR(1) model for residual, conditioning on previous residual $\epsilon_{i-1,j}$

$$\epsilon_{ij} \;=\; \alpha\epsilon_{i-1,j} + \delta_{ij}, \qquad \delta_{ij} \sim \mathrm{N}(0,\sigma^2) \quad \mathrm{Cor}(\epsilon_{i-1,j}, \delta_{ij}) = 0$$

- Correlation structure is

$$\mathrm{Cor}(\epsilon_{ij}, \epsilon_{i'j}) \;=\; \alpha^{|t_{ij} - t_{i'j}|}, \quad |\alpha| < 1$$

Dropout and missing data

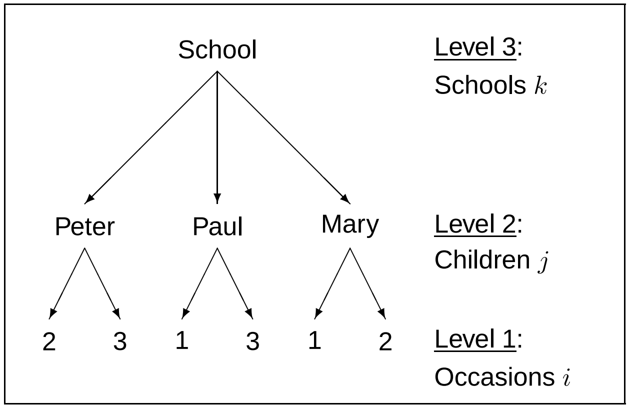
- Dropout or attrition is common where subjects are lost to follow-up from some time onwards (monotone missingness)
- Intermittent missing data also occur (e.g., subjects miss appointments but return)
- Old-fashioned methods & software (e.g., repeated measures ANOVA in SPSS) use listwise deletion, where all subjects with incomplete data are dropped
- Multilevel modeling & other modern methods (& modern software) use all available data
- Depending on reasons for dropout and missing data and on estimation method, both approaches can give inconsistent estimates

Types of missing data

- Missing completely at random (MCAR):
  $\Longrightarrow$ consistent estimates from ‘listwise’ data but inefficient
- Covariate-dependent dropout
  $\Longrightarrow$ consistent estimates if covariates that relate to missingness are included in model
- Missing at random (MAR):
  probability of missingness can depend on covariates and observed responses
  $\Longrightarrow$ consistent estimates if maximum likelihood used and model correctly specified
- Not missing at random (NMAR):
  probability of missingness depends on what that response would have been
  $\Longrightarrow$ Problems with all methods; can attempt to model missingness

Three-level data

- Units i nested in clusters j nested in superclusters k
  e.g. occasions i in children j in schools k

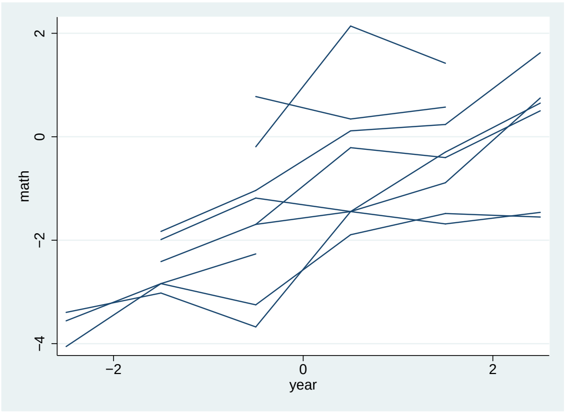


Example: Sustaining effects study

- Longitudinal survey of children in the six primary school years
- Primary sampling units were urban public primary schools
- 60 schools, 1721 students, 6 panel waves
- Variables:
  - Level 1 (occasion)
    - [Math]: Math test score from item response model y_{ijk}
    - [Year]: Year of study minus 3.5 a_{1ijk}
      (values -2.5, -1.5, -0.5, 0.5, 1.5, 2.5)
  - Level 2 (child)
    - [Black]: Dummy variable for being African American x_{1jk}
    - [Hispanic]: Dummy variable for being Hispanic x_{2jk}
  - Level 3 (school)
    - [Lowinc]: Percentage of students from low income families w_{1k}

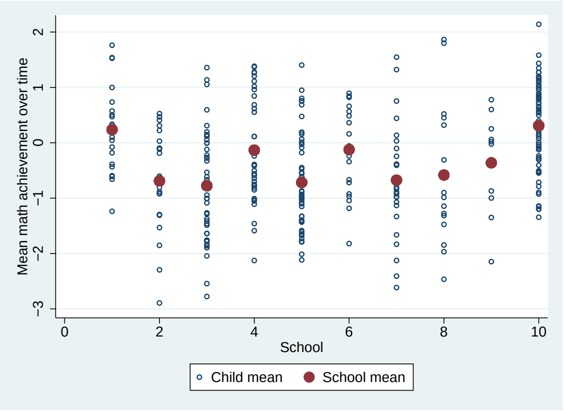
Variability between and within children

- Observed growth trajectories for 9 children from the same school



Variability between and within schools

- Mean math score over time for children from 10 schools



Three-level model

$$
\begin{aligned}
y_{ijk} &= \beta_1 + \beta_2 w_{1k} + \beta_3 x_{1jk} + \beta_4 x_{2jk} \\
&+ \beta_5 a_{1ijk} + \underbrace{\beta_6 w_{1k} a_{1ijk} + \beta_7 x_{1jk} a_{1ijk} + \beta_8 x_{2jk} a_{1ijk}}_{\text{Interactions}} \\
&+ \underbrace{\zeta_{1jk}^{(2)} + \zeta_{2jk}^{(2)} a_{1ijk}}_{\text{Child}} + \underbrace{\zeta_{1k}^{(3)} + \zeta_{2k}^{(3)} a_{1ijk}}_{\text{School}} + \underbrace{\epsilon_{ijk}}_{\text{Occ.}}
\end{aligned}
$$

Maximum likelihood estimates

Fixed part

		Est	(SE)
$\beta_1 \equiv \gamma_{000}$	[Cons]	0.141	(0.127)
$\beta_2 \equiv \gamma_{001}$	[Lowinc]	−0.008	(0.002)
$\beta_3 \equiv \beta_{01}$	[Black]	−0.502	(0.078)
$\beta_4 \equiv \beta_{02}$	[Hispanic]	−0.319	(0.086)
$\beta_5 \equiv \gamma_{100}$	[Year]	0.875	(0.039)
$\beta_6 \equiv \gamma_{101}$	[Lowinc]×[Year]	−0.001	(0.000)
$\beta_7 \equiv \beta_{11}$	[Black]×[Year]	−0.031	(0.022)
$\beta_8 \equiv \beta_{12}$	[Hispanic]×[Year]	0.043	(0.025)

Random part

	Est
$\sqrt{\psi_{11}^{(2)}}$	0.789
$\sqrt{\psi_{22}^{(2)}}$	0.105
$\rho_{21}^{(2)}$	0.561
$\sqrt{\psi_{11}^{(3)}}$	0.279
$\sqrt{\psi_{22}^{(3)}}$	0.089
$\rho_{21}^{(3)}$	0.033
$\sqrt{\theta}$	0.55

Interpretation of estimates

- In the middle of primary school, controlling for school mean income,
  - black and Hispanic children score on average 0.50 points and 0.32 points lower than white children, respectively
  - within ethnic groups, children's mean scores have a standard deviation of 0.79 within schools and 0.28 between schools; the standard deviation of scores around child-specific regression lines is 0.55
- On average, the mean math score increases 0.88 points per year for white children in schools with no low income children and this increase does not differ significantly for blacks or Hispanics
- The average annual increase in mean math scores is somewhat lower in schools with low income children, for a given ethnicity
- After controlling for ethnicity and school mean income, the average annual increase in math scores has a within-school standard deviation of 0.11 and a between-school standard deviation of 0.09

Model using three-stage (R&B) formulation

- Level-1 model:

$$y_{ijk} = \pi_{0jk} + \pi_{1jk} a_{1ijk} + e_{ijk}$$

  - Linear growth model
- Level-2 models:

$$\pi_{pjk} = \beta_{p0k} + \beta_{p1} x_{1jk} + \beta_{p2} x_{2jk} + r_{pjk}, \quad p = 0, 1$$

  - Mean intercept and slope depend on [Black] and [Hispanic]
  - Intercept and slope vary randomly between students within ethnic groups
- Level-3 models:

$$\beta_{p0k} = \gamma_{p00} + \gamma_{p01} w_{1k} + u_{p0k}, \quad p = 0, 1$$

  - Mean intercept and slope depend on [Lowinc]
  - Intercept and slope vary randomly between schools with given [Lowinc]

Deriving the reduced form

- Substitute level-3 models into level-2 models

$$\begin{aligned}\pi_{pjk} &= \underbrace{\gamma_{p00} + \gamma_{p01} w_{1k} + u_{p0k}}_{\beta_{p0k}} + \beta_{p1} x_{1jk} + \beta_{p2} x_{2jk} + r_{pjk} \\ &= \gamma_{p00} + \gamma_{p01} w_{1k} + u_{p0k} + \beta_{p1} x_{1jk} + \beta_{p2} x_{2jk} + r_{pjk}, \quad p = 0, 1\end{aligned}$$

- Substitute level-2 models into level-1 model

$$\begin{aligned}y_{ijk} &= \underbrace{\gamma_{000} + \gamma_{001} w_{1k} + u_{00k} + \beta_{01} x_{1jk} + \beta_{02} x_{2jk} + r_{0jk}}_{\pi_{0jk}} \\ &\quad + \underbrace{(\gamma_{100} + \gamma_{101} w_{1k} + u_{10k} + \beta_{11} X_{1jk} + \beta_{12} X_{2jk} + r_{1jk})}_{\pi_{1jk}} a_{1ijk} + e_{ijk} \\ &= \gamma_{000} + \gamma_{001} w_{1k} + \beta_{01} x_{1jk} + \beta_{02} x_{2jk} \\ &\quad + \gamma_{100} a_{1ijk} + \gamma_{101} w_{1k} a_{1ijk} + \beta_{11} x_{1jk} a_{1ijk} + \beta_{12} x_{2jk} a_{1ijk} \\ &\quad + r_{0jk} + r_{1jk} a_{1ijk} + u_{00k} + u_{10k} a_{1ijk} + e_{ijk}\end{aligned}$$

Further reading

-  Rabe-Hesketh & Skrondal (2012): Applied multilevel modeling (MLM) using Stata
- Snijders & Bosker (2011): Excellent introduction to MLM
- Fitzmaurice, Laird & Ware (2011): Most accessible biostatistical book on longitudinal data analysis (LDA)
- Wooldridge (2010): Most accessible econometric book on LDA
- Goldstein (2010): Generalized linear mixed models (GLMM)
- Raudenbush & Bryk (2002): GLMM
- McCulloch, Searle & Neuhaus (2008): Theoretical treatment of LMMs and GLMMs
-  Skrondal & Rabe-Hesketh (2004): GLMM & Generalized latent variable modeling