Sensitivity Analysis of Mixed-Effects Models When Longitudinal Data are Incomplete

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Overview

- Mixed-effects models for longitudinal data
- Missing data in longitudinal studies
- Sensitivity analysis
- Non-ignorable methods
- Example

Mixed-effects models for longitudinal data

- Flexible methodology
  - Different types of response distributions
  - Different mathematical functions to describe a growth process
  - Individual-specific times of measurement
  - Missing data

Meeting challenges of missing data in longitudinal data analysis

- Mixed-effects models allow for person-specific patterns of data collection
  - Unique times of measurement for individuals
  - Individuals need not be observed same number of times
- Thus, missing data are often easily handled, technically speaking

Types of missing data

- Three types based on 'missingness'
  - Missingness: Whether or not data are missing
- Missing completely at random (MCAR) (Rubin, 1976)
  - Missingness independent of observed and missing data
  - Special case of MCAR
    - Little (1995) 'covariate-dependent dropout'
    - Missing data depend on covariates, not observed outcome response
- Missing at random (MAR)
  - Missingness independent of missing data
    - Missingness depends only on observed data
      - E.g., response observed prior to drop-out as well as covariates
    - Diggle and Kenward (1994) 'random drop-out'
- Missing not at random (MNAR)
  - Missingness dependent on missing data
    - Conditional on observed data, mechanism depends on missing data

Missing data in mixed-effects models

- Under a mixed-effects model with maximum likelihood estimation
  - Missing data are assumed to be MAR
- Missingness may depend on
  - observed values of longitudinal response
  - observed covariates included in the model
- Missing data are MAR if, conditional on the observed data, missingness is independent of missing data

Testing assumption of MAR

- Cannot be empirically tested
  - The missing data are not available for study
  - The mechanism giving rise to the missing data is not typically known
  - Thus, not possible to test the assumption that the two are independent

Missing data that are not ignorable

- A least restrictive assumption
  - Missingness, conditional on observed data, is *dependent* on the missing data
  - If missing data are MNAR, missingness should not be ignored under a mixed-effects model
  - Indeed, statistical inference may be invalid when missing data are MNAR and the missingness is not addressed by the model
- Similar to MAR, MNAR cannot be empirically tested

Sensitivity analysis

- Commonly used in study of missing data under a mixed-effects model when missing data are not ignorable
- Sensitivity analysis
  - General approach to assess how changes in data or a model may influence statistical inference
  - E.g.,. Study how the data of an individual may influence the parameter estimates of a model

Strategy for a sensitivity analysis

- MNAR frameworks
  - Selection model
  - Pattern-mixture random-effects model
  - Shared parameter model
- In practice, missing data process not often known
- So, decision of how a missing data process should be specified in a given situation can be difficult
- By considering multiple frameworks for the missing data process, avoid complete reliance on any single method
- Further, within methods, variations of how to specify the missing data process are possible

Note

- In practice, likely many missing data patterns
  - Intermittently missing data
  - Missing data due to subject attrition
- Here, consider subject attrition
  - Intermittently missing data assumed ignorable
- It may be that in some situations intermittently missing data are not ignorable and a different modeling strategy ought to be adopted

A starting point

- Assume a full data set with some missing observations
  - Let $Y = \{Y^0, Y^m\}$
    - Y^0 → observed data
    - Y^m → missing data
  - Let R denote missingness
    - R = 1 if Y is observed
    - R = 0 if Y is missing
- Assuming informative missing data process, Y and R may be considered together

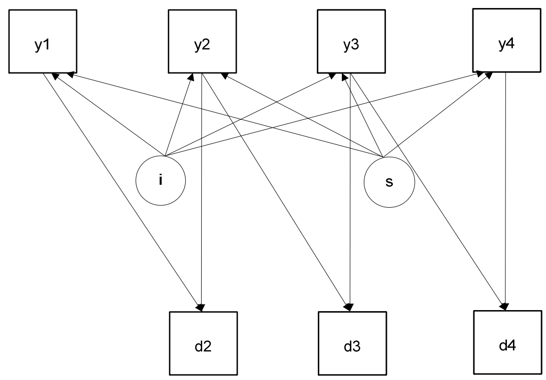
Full data density

- $f(y_i, r_i \mid X_i, W_i, \theta, \psi)$
  - X_i design matrix for y_i
  - W_i design matrix for r_i
  - θ model parameters for y_i
  - ψ model parameters for r_i
- MNAR frameworks
  - Based on different factorizations of the full density

Selection model

- $f(y_i \mid X_i, \theta)\, f(r_i \mid y_i, W_i, \psi)$
  - Missing data depend on longitudinal response
  - Indicators represent missing data process
    - E.g., let *d* be an indicator of dropout
- Longitudinal response
  - Linear mixed model (Diggle & Kenward,1994)
  - Partially nonlinear mixed model (Xu & Blozis, *in press*)
- Missing data indicators
  - Logistic regression (Diggle & Kenward, 1994)

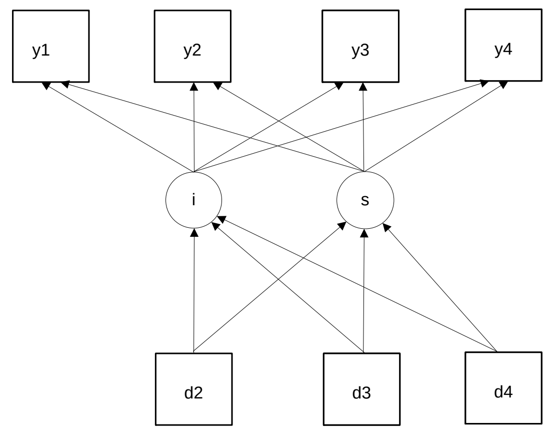
Selection model
(d's are indicators of dropout at waves 2, 3 and 4)



Pattern-mixture random-effects models

- $f(y_i \mid r_i, X_i, \theta)\ f(r_i \mid W_i, \psi)$
- Indicator variables represent missing data patterns
  - E.g., d = 1 if dropout; d = 0 otherwise
- Longitudinal response depends on indicators of missing data patterns
- Hedeker & Gibbons (1997)
  - Longitudinal response: Linear mixed model
  - Growth coefficients moderated by missing data patterns

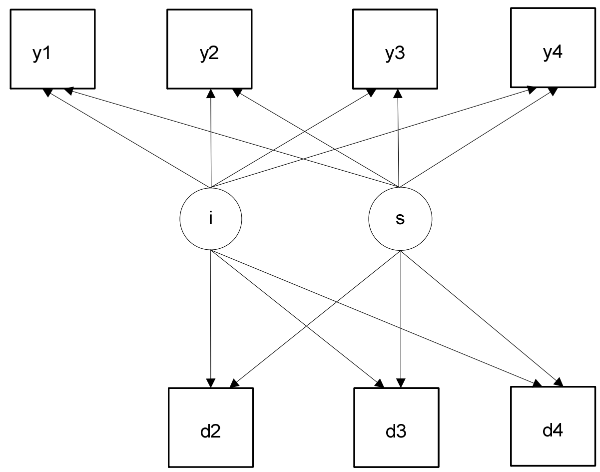
Pattern-mixture random-effects models (d's are indicators of missing data patterns)



Shared parameter model

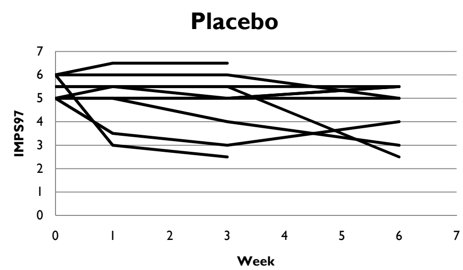
- $f(y_i \mid r_i, X_i, \theta, b_i)\ f(r_i \mid W_i, \psi, b_i)$
- Longitudinal response model and missing data model are assumed to depend on a shared latent variable or random effect
- Common specification (Follmann & Wu, 1995)
  - Conditional on random effects, Y and R are independent

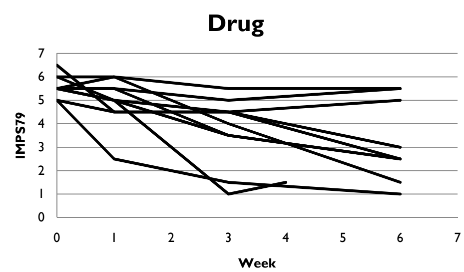
Shared Parameter Model
(d's are indicators of dropout at waves 2, 3 and 4)



Example: Illness severity ratings

- Data
  - National Institute of Mental Health Schizophrenia Collaborative Study
  - see Hedeker & Gibbons, 1997, references therein
- *N* = 437 psychiatric patients randomly assigned to groups
  - placebo (n=108)
  - psychiatric medication (n=329)
- A 7-point ordinal-scaled illness severity rating (IMPS97)
  - 1 = normal … 7 = most severe illness rating
  - Weekly ratings following study onset : 0,1,2,3,4,5,6
  - Treat score as continuous
- Subject attrition
  - Dropout defined as whether or not patient dropped by final measurement wave
  - *Dropout* = 1 if individual dropped
  - *Dropout* = 0 otherwise
    - Placebo: Of n = 108, 70 (65%) 'completer'
    - Drug: Of n = 329, 265 (81%) 'completer'





Longitudinal Model

- Series of models fitted
  - No growth
  - Linear growth
  - Linear growth based on square root of time
  - Quadratic growth
  - Exponential

Longitudinal response: Model fit

Growth Function	-2lnL	p	AIC
No change	5668.2	3	5674.2
Linear	4874.2	6	4886.2
Linear by square of time	4720.5	6	4732.5
Quadratic	4699.7	10	4719.7
Exponential	4668.0	10	4688.0

- All models include random effects on growth coefficients
- Time-specific errors assumed to be independent between weeks with constant variance

Exponential growth model

- $f = \beta_1 - (\beta_1 - \beta_0)\exp\{-\beta_2(week_j)\}$
  - $\beta_0 \rightarrow$ initial response
  - $\beta_1 \rightarrow$ potential response
  - $\beta_2 \rightarrow$ change rate
- Note
  - Drug condition is important in the study of these data
  - Ignored here to simplify presentation

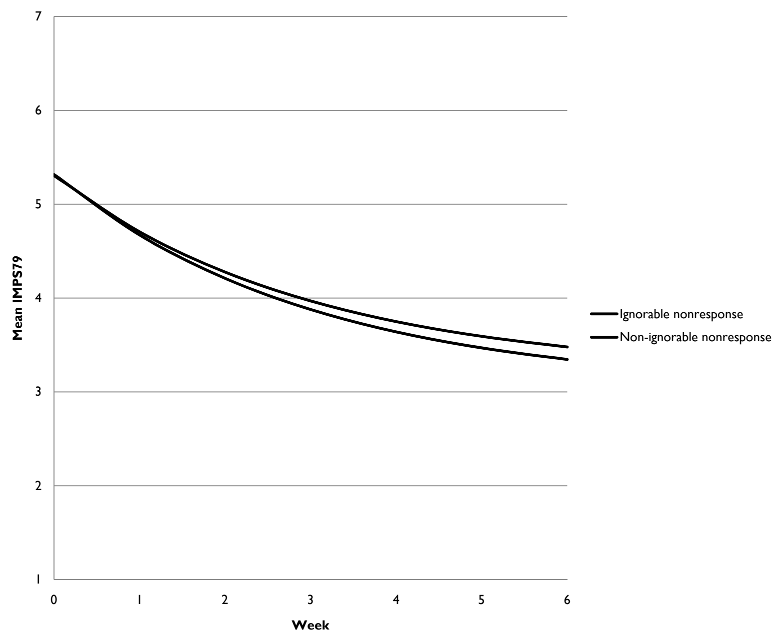
Selection model

- Longitudinal response follows exponential function
- *Dropout*
  - Logit of probability of dropout at $time_j$ regressed on y_{j-1} and y_j
  - $Logit[P(d = j \mid d \geq j)] = \psi_0 + \psi_1 y_{j-1} + \psi_2 y_j$
- If $\psi_1 = 0, \psi_2 = 0$ → dropout ignorable
- If $\psi_2 = 0$ → dropout ignorable
- If $\psi_2 \neq 0$ → dropout not ignorable

Selection model: Results

Missingness	-2lnL	AIC
MCAR	7385.0	7407.0
MAR	7369.5	7393.5
MNAR	7355.2	7381.2

- Deviance test comparing MCAR and MAR → MAR preferred
- MNAR: Neither deviance test nor test of parameter estimate relating to non-ignorable dropout is reliable (Jansen et al., 2006)



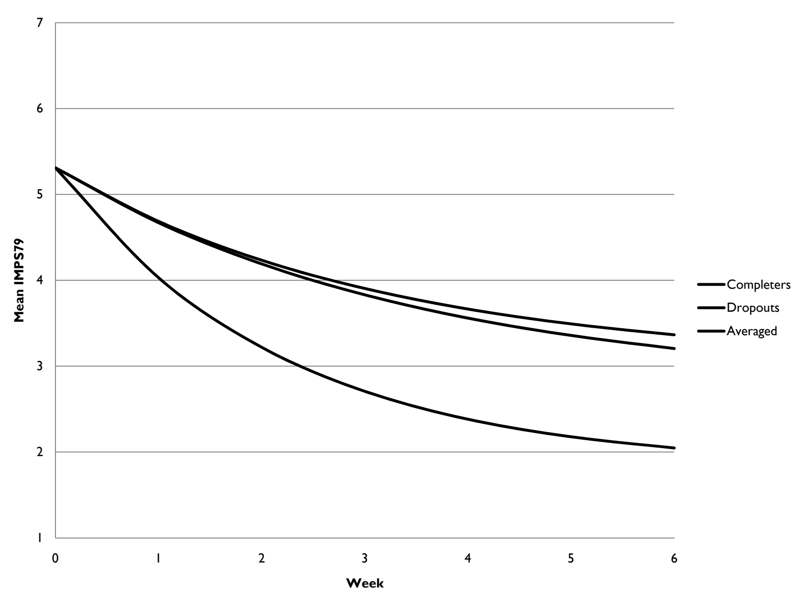
Pattern-mixture random-effects model

- Longitudinal response follows exponential growth function
- *Dropout* assumed to moderate growth coefficients
  - $\beta_{0i} = \gamma_{00} + \gamma_{01}\text{Dropout}_i + r_{0i}$
  - $\beta_{1i} = \gamma_{10} + \gamma_{11}\text{Dropout}_i + r_{1i}$
  - $\beta_{2i} = \gamma_{20} + \gamma_{21}\text{Dropout}_i + r_{2i}$

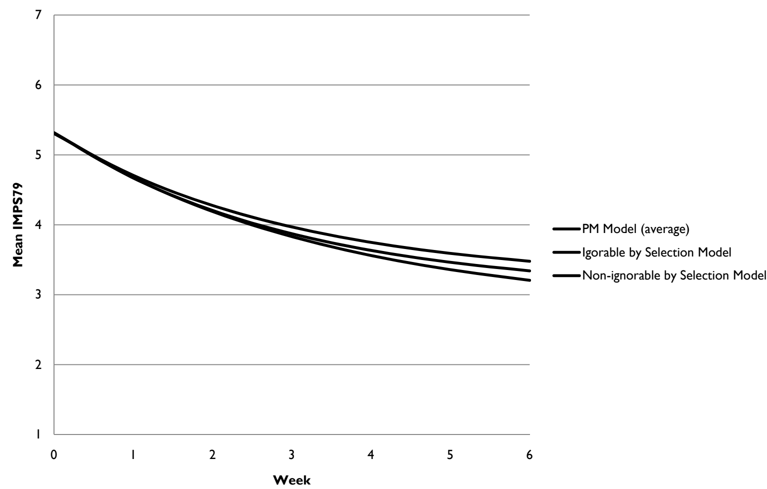
Pattern-mixture random-effects model: Results

Dropout	-2lnL	AIC
Moderates β_{0i}, β_{1i}, β_{2i}	4654.6	4680.6
Moderates β_{1i}, β_{2i}	4654.8	4678.8

- Potential response and change rate vary by pattern of dropout



Estimated mean trajectories based on different assumptions about missing data



Conclusions

- Pattern-mixture random-effects model
  - Allows for study of response by pattern of missingness
  - Compare completers to dropouts
  - Possible to produce averaged response
- Selection model
  - Some flexibility in how to model missing data mechanism
- Here, conclusions are the same about the form of the mean response

Comments

- Assumptions of MAR and MNAR cannot be tested empirically
- Several approaches to evaluating the sensitivity of the parameters of a longitudinal model
- Preferable to consider a few, not to rely on any one method
- Keep in mind
  - Missing data mechanism often not known
  - Even if sensitivity analysis suggests the longitudinal model is not sensitive to assumptions made about the missing data, not conclusive that true mechanism is ignorable

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