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 $Y = \{Y^0, Y^m\}$
    - $Y^0 \rightarrow$ observed data
    - $Y^m \rightarrow$ 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

- $f(y_i, r_i | X_i, W_i, \theta, \psi)$
  - $X_i$ design matrix for $y_i$
  - $W_i$ design matrix for $r_i$
  - $\theta$ model parameters for $y_i$
  - $\psi$ model parameters for $r_i$

- MNAR frameworks
  - Based on different factorizations of the full density

Selection model

- $f(y_i | X_i, \theta) \cdot f(r_i | y_i, W_i, \psi)$
  - 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
  - \( \text{Dropout} = 1 \) if individual dropped
  - \( \text{Dropout} = 0 \) 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

<table>
<thead>
<tr>
<th>Growth Function</th>
<th>-2lnL</th>
<th>p</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>5668.2</td>
<td>3</td>
<td>5674.2</td>
</tr>
<tr>
<td>Linear</td>
<td>4874.2</td>
<td>6</td>
<td>4886.2</td>
</tr>
<tr>
<td>Linear by square of time</td>
<td>4720.5</td>
<td>6</td>
<td>4732.5</td>
</tr>
<tr>
<td>Quadratic</td>
<td>4699.7</td>
<td>10</td>
<td>4719.7</td>
</tr>
<tr>
<td>Exponential</td>
<td>4668.0</td>
<td>10</td>
<td>4688.0</td>
</tr>
</tbody>
</table>

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

Exponential growth model

\[ f = \beta_1 - (\beta_1 - \beta_0) \exp{-\beta_2(\text{week}_j)} \]

- \( \beta_0 \rightarrow \) 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 $t_j$ regressed on $y_{j-1}$ and $y_j$
  - $\text{Logit}[P(d = j \mid d \geq j)] = \psi_0 + \psi_1 y_{j-1} + \psi_2 y_j$

- If $\psi_1 = 0, \psi_2 = 0 \rightarrow$ dropout ignorable
- If $\psi_2 = 0 \rightarrow$ dropout ignorable
- If $\psi_2 \neq 0 \rightarrow$ dropout not ignorable

**Selection model: Results**

<table>
<thead>
<tr>
<th>Missingness</th>
<th>-2lnL</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCAR</td>
<td>7385.0</td>
<td>7407.0</td>
</tr>
<tr>
<td>MAR</td>
<td>7369.5</td>
<td>7393.5</td>
</tr>
<tr>
<td>MNAR</td>
<td>7355.2</td>
<td>7381.2</td>
</tr>
</tbody>
</table>

- Deviance test comparing MCAR and MAR $\rightarrow$ 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

<table>
<thead>
<tr>
<th>Dropout</th>
<th>-2lnL</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderates $\beta_0, \beta_1, \beta_2$</td>
<td>4654.6</td>
<td>4680.6</td>
</tr>
<tr>
<td>Moderates $\beta_1, \beta_2$</td>
<td>4654.8</td>
<td>4678.8</td>
</tr>
</tbody>
</table>

- 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

References

- Heckman, J. (1976). The common structure of statistical models of truncation, sample selection and limited dependent variables, and a simple estimator for such models. Annals of Economic and Social Measurement, 5, 475-492.