A Simulation Study Comparing Weighted Estimating Equations and Multiple Imputation Based Estimating Equations

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Overview

- Generalized Estimating Equations (GEE)
- GEE in the Presence of Missing Data
  - Weighted Estimating Equations (WGEE)
  - Multiple Imputation based Estimating Equations (MI-GEE)
- Design of Simulation Study
  - Asymptotic Simulation
  - Finite Sample Simulation
- Results
- Discussion & Conclusions
- Further Research
Generalized Estimating Equations

- Liang & Zeger (1986)
- extension of Generalized Linear Models (GLMs) to account for correlated responses
- allows estimation of regression and association parameters without specifying the entire likelihood
- not a full likelihood procedure in the sense that specification is restricted to the first moment only

Score Equations:

\[ S(\beta) = \sum_{i=1}^{N} D_i^T V_i(\alpha)^{-1} (y_i - \mu_i) = 0 \]

where:

\[ D_i = \left[ \frac{\partial \mu_{ij}}{\partial \beta} \right] \]

and

\[ V_i(\beta, \alpha) = \phi A_i^{1/2}(\beta) R_i(\alpha) A_i^{1/2}(\beta) \]
The estimators of $\beta$ are consistent even if the working correlation matrix is incorrect.

A poor choice of working correlation matrix can affect the efficiency of the estimators of $\beta$. 

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A poor choice of working correlation matrix can affect the efficiency of the estimators of $\beta$. 

"Sandwich" or empirically-corrected variance estimator
GEE in the Presence of Missing Data

2 Approaches

• WGEE

• MI-GEE
Weighted GEE

- Robins, Rotnitzky & Zhao (1995)
- modification to standard GEE to address missingness in the data
- modification is done via a weighting scheme
  - weights obtained from dropout model
  - weights: inverse of dropout probability
  - higher dropout probability $\rightarrow$ lower weight
- standard GEE is simply applied with weights
WGEE: Procedure

• Dropout model for missingness

\[ v_{id_i} = P(D = d_i) = \prod_{k=2}^{d_i-1} \left[ 1 - P(R_{ik} = 0 | R_{i2} = \ldots = R_{i,k-1} = 1) \right] \times \]

\[ \left[ P(R_{id_i} = 0 | R_{i2} = \ldots = R_{i,d_i-1} = 1) \right]^{I(d_i \leq T)} \]

• Measurement model for outcomes

\[ \text{same as in standard GEE} \]

* Dropout model is combined with measurement model via weights

\[ S(\beta) = \sum_{i=1}^{N} \frac{1}{v_{id_i}} D_i' [V_i(\alpha)]^{-1} (y_i - \mu_i) = 0 \]
Multiple Imputation GEE

- Rubin (1987)
- entails 'filling in' missing data with plausible values
- solves the missing-data problem at the beginning of the analysis
- Monte Carlo technique in which missing values are replaced by \( m>1 \) simulated versions
- has become popular in biomedical, behavioral and social science research where investigations are hindered by missing data
MI-GEE: Procedure

1. **Imputation Stage**
   Impute missing values $m$ times using some imputation model.

2. **Analysis Stage**
   Analyze each of the $m$ completed data sets using the analysis model of choice, e.g., GEE.

3. **Pooling Stage**
   Pool the $m$ sets of analyses into a single analysis using multiple imputation principles.
Data Setup

- binary response
- 3 time points
- 2 groups (e.g., treatment vs. placebo)
- 3 missingness patterns (dropout type)
Data Generation

3 Generation Models

1. GMI
   - Measurement model: Bahadur
   - Dropout model: MAR dropout

2. GMII
   - Measurement model: Conditional AR(2)
   - Dropout model: MAR dropout

3. GMIII
   - Measurement model: Gaussian
   - Dropout model: MAR dropout
Asymptotic Simulation

- 2 (binary) outcomes at 3 time points $\rightarrow 2^3 = 8$
- 3 missingness patterns $\rightarrow 8 \times 3 = 24$
- 2 groups $\rightarrow 24 \times 2 = 48$
- for multiple imputations: $M = 500$

- 48 possibilities, each weighted by the probabilities obtained from the either GMI or GMII
Finite-Sample Simulation

- $n_1 = n_2 = 50$ for each group
- $N = n_1 + n_2 = 100$ for each sample
- $S = 500$ samples
- generated from GMIII
- for multiple imputations: $M = 5$

- (Gaussian) continuous outcome dichotomized to obtain the binary outcome
Results for GMI
Asymptotic Simulation: Correct Mean Structure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WGEE</th>
<th>MI-GEE</th>
<th>Standard GEE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias</td>
<td>Relative Bias</td>
<td>Bias</td>
</tr>
<tr>
<td>Intercept</td>
<td>–7.408 E–10</td>
<td>2.963 E–09</td>
<td>0.1739</td>
</tr>
<tr>
<td>x</td>
<td>–2.423 E–09</td>
<td>–4.846 E–09</td>
<td>–0.8166</td>
</tr>
<tr>
<td>time</td>
<td>3.939 E–10</td>
<td>1.970 E–09</td>
<td>–0.1585</td>
</tr>
<tr>
<td>x*time</td>
<td>3.932 E–10</td>
<td>–4.915 E–10</td>
<td>0.7556</td>
</tr>
</tbody>
</table>
Results: Correct Mean Structure

GMI: BAHADUR + MAR Dropout

Probability, $P(Y=1)$ vs. Time

- $trt=0$ TRUE/WGEE
- $trt=1$ TRUE/WGEE
- $trt=0$ MI-GEE
- $trt=1$ MI-GEE
- $trt=0$ GEE
- $trt=1$ GEE
# Results for GMI

## Asymptotic Simulation: Incorrect Mean Structure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WGEE</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias</td>
<td>Relative Bias</td>
<td>Bias</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.5756</td>
<td>–2.3022</td>
<td>0.2046</td>
</tr>
<tr>
<td>x</td>
<td>–1.2618</td>
<td>–2.5236</td>
<td>–0.8957</td>
</tr>
<tr>
<td>time</td>
<td>–0.3552</td>
<td>–1.7759</td>
<td>–0.1743</td>
</tr>
<tr>
<td>x*time</td>
<td>0.8000</td>
<td>–1.0000</td>
<td>0.8000</td>
</tr>
</tbody>
</table>
Results: Incorrect Mean Structure

GMI: BAHADUR + MAR Dropout
# Results for GMII

## Asymptotic Simulation: Correct Mean Structure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WGEE</th>
<th>MI-GEE†</th>
<th>Standard GEE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias</td>
<td>Relative Bias</td>
<td>Bias</td>
</tr>
<tr>
<td>Intercept</td>
<td>−0.0633</td>
<td>0.1729</td>
<td>0.0899</td>
</tr>
<tr>
<td>x</td>
<td>−0.0556</td>
<td>−0.2082</td>
<td>0.1346</td>
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<tr>
<td>time</td>
<td>0.0380</td>
<td>0.1677</td>
<td>−0.0988</td>
</tr>
<tr>
<td>x*time</td>
<td>0.0352</td>
<td>0.4459</td>
<td>−0.1693</td>
</tr>
</tbody>
</table>

† Marginalized from conditional AR(2) logistic model
Results: Correct Mean Structure

GMII: AR(2) + MAR Dropout

[Graph showing the comparison of different models (trt=0 TRUE, trt=1 TRUE, trt=0 MI-GEE, trt=1 MI-GEE, trt=0 WGEE, trt=1 WGEE, trt=0 GEE, trt=1 GEE) over time (0 to 3) with probability P(Y=1) ranging from 0.30 to 0.80.]
## Results for GMII

### Asymptotic Simulation: Incorrect Mean Structure

<table>
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<th>MI-GEE†</th>
<th>Standard GEE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias</td>
<td>Relative Bias</td>
<td>Bias</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.6596</td>
<td>–1.8031</td>
<td>0.1798</td>
</tr>
<tr>
<td>x</td>
<td>–1.0825</td>
<td>–4.0498</td>
<td>–0.0458</td>
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<tr>
<td>time</td>
<td>–0.3417</td>
<td>–1.5087</td>
<td>–0.1437</td>
</tr>
<tr>
<td>x*time</td>
<td>–0.0790</td>
<td>–1.0000</td>
<td>–0.0790</td>
</tr>
</tbody>
</table>

† Marginalized from conditional AR(2) logistic model
Results: Incorrect Mean Structure

GMII: AR(2) + MAR Dropout

Probability, P(Y=1)

0.20 0.30 0.40 0.50 0.60 0.70 0.80

0 0.5 1 1.5 2 2.5 3

Time

trt=0 TRUE  trt=1 TRUE
trt=0 MI-GEE  trt=1 MI-GEE
trt=0 WGEE  trt=1 WGEE
trt=0 GEE  trt=1 GEE
## Results for GMIII

### Finite-Sample Simulation Results†: Correct Mean

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WGEE</th>
<th></th>
<th>MI-GEE</th>
<th></th>
<th>Standard GEE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias</td>
<td>MSE</td>
<td>Bias</td>
<td>MSE</td>
<td>Bias</td>
<td>MSE</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.2317</td>
<td>0.3429</td>
<td>0.00057</td>
<td>0.1926</td>
<td>–0.0243</td>
<td>0.2087</td>
</tr>
<tr>
<td>x</td>
<td>–0.0411</td>
<td>0.5526</td>
<td>0.00636</td>
<td>0.3919</td>
<td>–0.0172</td>
<td>0.4426</td>
</tr>
<tr>
<td>time</td>
<td>0.0387</td>
<td>0.0847</td>
<td>0.00006</td>
<td>0.0584</td>
<td>0.0293</td>
<td>0.0688</td>
</tr>
<tr>
<td>x*time</td>
<td>0.0152</td>
<td>0.2016</td>
<td>–0.00646</td>
<td>0.1470</td>
<td>0.0150</td>
<td>0.1841</td>
</tr>
</tbody>
</table>

† Based on S=449 samples
Results: Correct Mean Structure

GMIII: GAUSSIAN + MAR Dropout
## Results for GMIII

### Finite-Sample Simulation Results †: Incorrect Mean

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WGEE</th>
<th></th>
<th>MI-GEE</th>
<th></th>
<th>Standard GEE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bias</td>
<td>MSE</td>
<td>Bias</td>
<td>MSE</td>
<td>Bias</td>
<td>MSE</td>
</tr>
<tr>
<td>Intercept</td>
<td>0.0652</td>
<td>0.5225</td>
<td>–0.2572</td>
<td>0.2836</td>
<td>–0.2840</td>
<td>0.5165</td>
</tr>
<tr>
<td>x</td>
<td>0.8203</td>
<td>0.8226</td>
<td>0.9178</td>
<td>0.9147</td>
<td>0.8989</td>
<td>0.9411</td>
</tr>
<tr>
<td>time</td>
<td>0.1539</td>
<td>0.1504</td>
<td>0.1535</td>
<td>0.0814</td>
<td>0.1889</td>
<td>0.1488</td>
</tr>
<tr>
<td>x*time</td>
<td>–0.7038</td>
<td>0.4953</td>
<td>–0.7038</td>
<td>0.4953</td>
<td>–0.7038</td>
<td>0.4953</td>
</tr>
</tbody>
</table>

† Based on S=500 samples
Results: Incorrect Mean Structure

GMIII: GAUSSIAN + MAR Dropout

Probability, P(Y=1) vs. Time

- trt=0 TRUE
- trt=1 TRUE
- trt=0 WGE
- trt=1 WGE
- trt=0 MI-GEE
- trt=1 MI-GEE
- GEE
- trt=0 GEE
- trt=1 GEE
Discussion & Conclusions

GMI: Bahadur + MAR dropout

• Correct Mean Structure
  ✅ WGEE gives asymptotically unbiased estimates
  ✅ MI-GEE yields biased estimates: imputation model does not match the dropout model of the GM
  ✅ GEE yields biased estimates but of small magnitudes

• Incorrect Mean Structure
  ✅ WGEE/GEE severely biased (as much as 2.5 times true value)
  ✅ MI-GEE gives least bias: robustness (?) to misspecification of mean
  ✅ WGEE and GEE give very comparable results: non-significant dropout parameter
Discussion & Conclusions

GMII: AR(2) + MAR dropout

- Correct Mean Structure
  - WGEE leads to least bias
  - GEE only slightly worse than WGEE
  - MI-GEE gives largest bias

- Incorrect Mean Structure
  - WGEE gives largest bias
  - MI-GEE better than GEE for some parameters

*Results may not be entirely comparable because of the marginalization of the conditional AR(2) GM.*
Discussion & Conclusions

GMIII: Gaussian + MAR dropout

- Correct Mean Structure
  - MI-GEE yields very small bias and smallest MSE: imputation model is correct
  - GEE performing better than WGEE (!): dropout parameter not significant in about half the samples (?)

- Incorrect Mean Structure
  - MI-GEE still outperforming WGEE/GEE in terms of bias and MSE
  - WGEE and GEE give comparable results: low percentages of incompleters in generated datasets
Discussion & Conclusions

- **WGEE**
  - performing as expected from the theory
  - requires correct specification of mean structure

- **MI-GEE**
  - seems more promising when imputing from a continuous outcome
  - requires correct specification of imputation model
  - seems robust to misspecification of the mean structure
Further Research

• Computation of asymptotic covariance
• Exploration of other parameter values
  ➥ dropout parameter: significant
• Comparison of methods under varying percentages of missingness
• Extension to more timepoints
• Exploration of more appropriate multivariate imputation models for binary outcome
  ➥ SAS PROC MI: univariate
