On Model Selections for Repeated Measurement Data in Clinical Research

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Outline

- Introduction
- Methods
- Simulation Study
- Application Example
- Discussions

Repeated Measurement Design

- Repeated Measurement Design:
  - Multiple responses of each experimental unit are collected at different time points or under different conditions

- Data Structure:

ID	Group	Time (month)	Outcome
1	0	0	2
1	0	6	4
1	0	12	9
2	1	0	5
2	1	6	3
2	1	12	4
⋮	⋮	⋮	⋮

Repeated Measurement Design (cont.)

- Applications
  - long term intervention efficacy
  - risk factors of chronic disease
- Benefits
  - experiments efficiencies
- Disadvantages
  - correlated responses
  - missing data

Repeated Measurement Design (cont.)

- Data Structure with Missing:

ID	Group	Time (month)	Outcome
1	0	0	NA
1	0	6	4
1	0	12	9
2	1	0	5
2	1	6	3
2	1	12	NA
3	1	0	6
⋮	⋮	⋮	⋮
⋮	⋮	⋮	⋮

Mixed Effects Model (Laird & Ware 1982)

- Takes longitudinal information and correlations among repeated measurements into account.
- Allow to evaluate and test the overall effect across every time point and the treatment effect at a fixed time point.
- Non-missing observations can help partially recover the lost information in the missing data.

Mixed Effects Model (cont.)

- Full Model:

$$
\begin{aligned}
Y_{ijk} &= \alpha_0 + \alpha_{Trt} I(i=1) + \sum_{k=1}^{T-1} \alpha_k I(Time = k) + \\
&\quad + \sum_{k=1}^{T-1} \alpha_{k+T-1} I(i=1) I(Time = k) + r_{ijk} + \epsilon_{ijk} \qquad (1)
\end{aligned}
$$

  - i: treatment assignment (1 for treated and 0 for untreated)
  - j: indexes an individual subject
  - k: measurement time point post baseline measurement $(=1, \cdots, T)$
  - Y_{ijk}: response change from baseline

Mixed Effects Model (cont.)

- Full Model:

$$
\begin{aligned}
Y_{ijk} &= \alpha_0 + \alpha_{Trt} I(i=1) + \sum_{k=1}^{T-1} \alpha_k I(Time = k) + \\
&\quad + \sum_{k=1}^{T-1} \alpha_{k+T-1} I(i=1) I(Time = k) + r_{ijk} + \epsilon_{ijk}
\end{aligned}
$$

  - α_0: intercept.
  - α_{Trt}: treatment effect (at last time point).
  - $\alpha_k (k = 1, \cdots, T-1)$: time effects.
  - $\alpha_{k+T-1} (k = 1, \cdots, T-1)$: time and treatment interactions.
  - r_{ijk}: cluster effects, i.e. $\mathbf{r}_{ij} \sim N(\mathbf{0}, \mathbf{\Sigma})$ with T $\times$ T dimension.
  - $\epsilon_{ijk} \sim N(0, \sigma^2)$: random error and $\epsilon_{ijk} \perp r_{ijk}$

Mixed Effects Model (cont.)

- Covariance Structure:

Unstructured Covariance Matrix:

$$\mathbf{\Sigma} = \begin{pmatrix} \sigma_1^2 & \sigma_{12} & \cdots & \sigma_{1T} \\ \sigma_{21} & \sigma_2^2 & \cdots & \sigma_{2T} \\ \vdots & \vdots & \ddots & \vdots \\ \sigma_{T1} & \sigma_{T2} & \cdots & \sigma_T^2 \end{pmatrix}$$

$\frac{T(T-1)}{2}$ covariance parameters, could be unstable

Compound Symmetry Covariance Matrix:

$$\mathbf{\Sigma} = \sigma^2 \begin{pmatrix} 1 & \rho & \cdots & \rho \\ \rho & 1 & \cdots & \rho \\ \vdots & \vdots & \ddots & \vdots \\ \rho & \rho & \cdots & 1 \end{pmatrix}$$

2 covariance parameters, strong assumptions

- Main Effects Model:

$$
\begin{aligned}
Y_{ijk} &= \alpha_0 + \alpha_{Trt} I(i=1) + \sum_{k=1}^{T-1} \alpha_k I(Time = k) + \\
&\quad + r_{ijk} + \epsilon_{ijk} \qquad (2)
\end{aligned}
$$

  - α_0: intercept.
  - α_{Trt}: treatment effect.
  - $\alpha_k (k = 1, \cdots, T-1)$: time effects.
  - r_{ijk}: cluster effects, i.e. $\mathbf{r}_{ij} \sim N(\mathbf{0}, \mathbf{\Sigma})$ with T $\times$ T dimension.
  - $\epsilon_{ijk} \sim N(0, \sigma^2)$: random error and $\epsilon_{ijk} \perp r_{ijk}$

Mixed Effects Model (Cont.)

- Null Model:

$$Y_{ijk} = \alpha_0 + \sum_{k=1}^{T-1} \alpha_k I(Time = k) + r_{ijk} + \epsilon_{ijk} \tag{3}$$

  - α_0: intercept.
  - $\alpha_k (k = 1, \cdots, T-1)$: time effects.
  - r_{ijk}: cluster effects, i.e. $\mathbf{r}_{ij} \sim N(\mathbf{0}, \mathbf{\Sigma})$ with T $\times$ T dimension.
  - $\epsilon_{ijk} \sim N(0, \sigma^2)$: random error and $\epsilon_{ijk} \perp r_{ijk}$

Treatment Effects

- Overall effects:

$$H_0 : \alpha_{Trt} = \alpha_T = \alpha_{T+1} = \cdots = \alpha_{2T-2} = 0 \;\; vs \;\; H_a : \text{Otherwise.}$$

- Effects at a fixed time point (usually at last time point):

$$H_0 : \alpha_{Trt} = 0 \;\; vs \;\; H_a : \alpha_{Trt} \neq 0$$

Treatment Effects Test

- Overall Effects:
  - likelihood ratio test:
    $\zeta_{LRT} = -2 \log \frac{\text{likelihood of null model (3) with UN}}{\text{likelihood of full model (1) with UN}} \sim \chi^2$
- Effects at Last Time Point:
  - t-test: $\zeta_T = \frac{\hat{\alpha}_{Trt,T}}{SE(\hat{\alpha}_{Trt,T})}$
  - full model (1) with UN: $\zeta_{FUN} = \frac{\hat{\alpha}_{Trt,FUN}}{SE(\hat{\alpha}_{Trt,FUN})}$

Model Selection

- Candidate Model Space:
  - Full and Main Effects Models
  - Covariance Structures
    - compound symmetry (CS)
    - autoregressive (AR)
    - unstructured (UN)
  - Candidate Models: full and main effects model with covariance structures
- Model Selection Criteria: BIC

Test Statistics for Treatment Effects

- Overall Effects:
  - model selection test statistics

$$\zeta_{MSA} = \begin{cases} \tilde{\boldsymbol{\alpha}}^{'}\boldsymbol{\Sigma}^{-1}\tilde{\boldsymbol{\alpha}} & \text{if } \hat{M} \in \text{ full model set (1)} \\ (\tilde{\alpha}_{Trt}/SE(\tilde{\alpha}_{Trt}))^2 & \text{if } \hat{M} \in \text{ main effects model set (2)} \end{cases}$$

$\tilde{\boldsymbol{\alpha}}^{'} = (\tilde{\alpha}_{Trt}, \tilde{\alpha}_T, \cdots, \tilde{\alpha}_{2T-2})$ is the MLE of $\boldsymbol{\alpha}^{'} = (\alpha_{Trt}, \alpha_T, \cdots, \alpha_{2T-2})$ from the optimal model $\hat{M}$ if it happens to be the full model (1), while $\tilde{\alpha}_{Trt}$ is the MLE of α_{Trt} from the optimal model $\hat{M}$ when it happens to be the main effects model (2)

$\boldsymbol{\Sigma}$ is the covariance matrix of $\tilde{\boldsymbol{\alpha}}^{'}$

Test Statistics for Treatment Effects

- Effects at Last Time Point:
  - model selection test statistics: $\zeta_{MSL} = \frac{\tilde{\alpha}_{Trt,\hat{M}}}{SE(\tilde{\alpha}_{Trt,\hat{M}})}$

Covariance Matrix Estimation Under Model Selection

- How to estimate $\boldsymbol{\Sigma}$?
  - Estimate of $\boldsymbol{\Sigma}$ is not trivial due to stochastic nature of model selection
  - Distribution of selecting a specific candidate model as the optimal model $\hat{M}$ is unknown $\Rightarrow$ bootstrapping

Restricted Cluster Bootstrapping Estimate of $\boldsymbol{\Sigma}$

- Simple bootstrap resampling does not work
- Restricted cluster bootstrap resampling

Step 1: Perform model selection on the observed dataset, D, to get the optimal model $\hat{M}$.

Step 2: Conduct **cluster level** resampling with replacement to get a resampled dataset and perform model selection on the resampled dataset D^b. Obtain the selected optimal model $\hat{M}^b$. If $\hat{M}^b = \hat{M}$, then the MLE of $\boldsymbol{\alpha}$, i.e. $\tilde{\boldsymbol{\alpha}}^b$, is used for the calculation of $\widehat{\boldsymbol{\Sigma}}_B$.

Step 3: Repeat Step 2 B times and calculate $\widehat{\boldsymbol{\Sigma}}_B$, i.e. the post-model selection covariance matrix estimate of $\tilde{\boldsymbol{\alpha}}$.

Restricted Cluster Bootstrapping Estimate of $\boldsymbol{\Sigma}$ (cont.)

$$\widehat{\boldsymbol{\Sigma}}_B = \frac{1}{B^* - 1} \sum_{b=1}^{B} (\tilde{\boldsymbol{\alpha}}^b - \bar{\boldsymbol{\alpha}}^b) \otimes (\tilde{\boldsymbol{\alpha}}^b - \bar{\boldsymbol{\alpha}}^b)' I(\hat{M}^b = \hat{M})$$

$\bar{\boldsymbol{\alpha}}^b = \frac{1}{B^*} \sum_{b=1}^{B} \tilde{\boldsymbol{\alpha}}^b I(\hat{M}^b = \hat{M})$.

$B^* = \sum_{b=1}^{B} I(\hat{M}^b = \hat{M})$.

Simulation Studies

- data model (no missing)

$$
\begin{aligned}
y_{ijk} \quad = \quad & -70 + 0.3 * I(i=1) + 4 * I(k=1) + 3 * I(k=2) \\
& +2 * I(k=3) + I(k=4) + \alpha_1 * I(i=1)I(k=1) \\
& +\alpha_2 * I(i=1)I(k=2) + \alpha_3 * I(i=1)I(k=3) \\
& +\alpha_4 * I(i=1)I(k=4) + r_{ijk} + \epsilon_{ijk}
\end{aligned}
$$

  - strong: $\alpha_1 = 0.45, \alpha_2 = 0.42, \alpha_3 = 0.39, \alpha_4 = 0.36$
  - moderate: $\alpha_1 = 0.24, \alpha_2 = 0.27, \alpha_3 = 0.33, \alpha_4 = 0.36$
  - weak: $\alpha_1 = 0.1, \alpha_2 = 0.075, \alpha_3 = 0.05, \alpha_4 = 0.025$
  - no interaction
  - random cluster effect $\mathbf{r}_{ij} \sim N(0, \mathbf{\Omega})$
  - $\epsilon_{ijk} \sim N(0, 1)$

Simulation Settings (Covariance Structures)

Covariance Structure (CS):

$$\boldsymbol{\Sigma} = \begin{pmatrix} 1 & 0.4 & 0.4 & 0.4 & 0.4 \\ & 1 & 0.4 & 0.4 & 0.4 \\ & & 1 & 0.4 & 0.4 \\ & & & 1 & 0.4 \\ & & & & 1 \end{pmatrix}$$

Table 1: Overall Treatment Effects Testing[a]

Data Model	Interaction	Statistics[b]	Power	Type I Error
Full (CS)	Strong	ζ_{LRT}	0.996	0.044
		ζ_{MSA}	1.000	0.048
	Moderate	ζ_{LRT}	0.967	0.044
		ζ_{MSA}	0.995	0.048
	Weak	ζ_{LRT}	0.621	0.044
		ζ_{MSA}	0.834	0.048
Main Effects (CS)	None	ζ_{LRT}	0.479	0.044
		ζ_{MSA}	0.710	0.048

a: results based on 1000 simulations with 100 subjects at each treatment arm
b: model selection via BIC with 200 bootstrap resampling
ζ_{LRT}: mixed effects model based likelihood ratio test for overall effects
ζ_{MSA}: model selection statistics for testing overall treatment effects

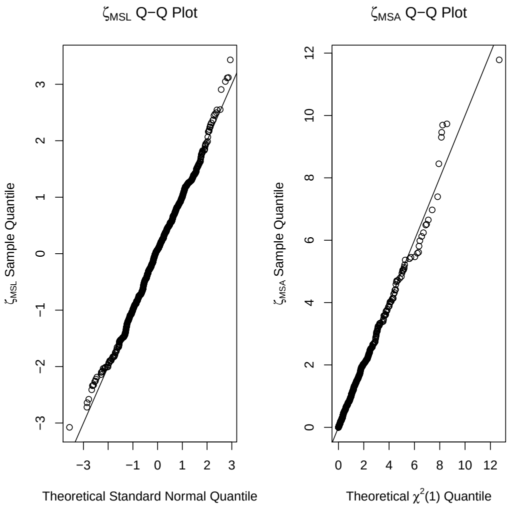
Simulation Results (Cont.)

Table 2: Last Time Point Treatment Effect Testing[a]

Data Model	Interaction	Statistics[b]	Power	Type I Error
Full (CS)	Strong	ζ_T	0.336	0.044
		ζ_{FUN}	0.343	0.046
		ζ_{MSL}	0.981	0.048
	Moderate	ζ_T	0.336	0.044
		ζ_{FUN}	0.343	0.046
		ζ_{MSL}	0.987	0.048
	Weak	ζ_T	0.336	0.044
		ζ_{FUN}	0.343	0.046
		ζ_{MSL}	0.834	0.048
Main Effects (CS)	None	ζ_T	0.336	0.044
		ζ_{FUN}	0.343	0.046
		ζ_{MSL}	0.710	0.048

Simulation Results (Cont.)

Figure 1: Model Selection Test Statistics Distributions Under the Null



Simulation Studies (cont.)

- Data Model (missing)

$$
\begin{aligned}
y_{ijk} &= -70 + 0.3 * I(i=1) + 0.3 * u_{ij} + 4 * I(k=1) \\
&\quad +3 * I(k=2) + 2 * I(k=3) + I(k=4) \\
&\quad +\alpha_1 * I(i=1)I(k=1) + \alpha_2 * I(i=1)I(k=2) \\
&\quad +\alpha_3 * I(i=1)I(k=3) + \alpha_4 * I(i=1)I(k=4) \\
&\quad +r_{ijk} + \epsilon_{ijk}
\end{aligned}
$$

  - $u_{ij} \sim Unif(-1, 1)$.
  - moderate: $\alpha_1 = 0.24, \alpha_2 = 0.27, \alpha_3 = 0.33, \alpha_4 = 0.36$
  - no interaction
  - random cluster effect $\mathbf{r}_{ij} \sim N(0, \boldsymbol{\Omega})$
  - $\epsilon_{ijk} \sim N(0, 1)$

Simulation Studies (cont.)

- Missing Mechanism:
  - to mimic controlled trial scenario: e.g. older age subjects in the treated group may miss measurements more frequently due to drug side-effects while younger subjects in the placebo group may miss measurement more frequently due to inefficacy of treatment, etc.
  - for the treatment arm 0 and one of the 1^{st} four time points k ($k = 1, 2, 3, 4$), five subjects with $u_{ij} > 0$ are randomly selected to have their observations set to missing, while for the treatment arm 1, 5 subjects with $u_{ij} < 0$ are randomly selected to create missing observations. For the last time point, we randomly select 10 subjects in the treatment arm 0 with $u_{ij} > 0.5$ and another 10 subjects from the treatment arm 1 with $u_{ij} < -0.5$ and set their observations to missing.
  - instead of imputing missing data, we analyze the simulated data with models (1), (3) and (2) except that we add baseline u_{ij} as a covariate into these models.

Simulation Settings (Covariance Structures)

Covariance Structure (CS):

$$\boldsymbol{\Sigma} = \begin{pmatrix} 1 & 0.4 & 0.4 & 0.4 & 0.4 \\ & 1 & 0.4 & 0.4 & 0.4 \\ & & 1 & 0.4 & 0.4 \\ & & & 1 & 0.4 \\ & & & & 1 \end{pmatrix}$$

- As a further comparison, when testing the last time point effect, we include the ANCOVA model test statistics $\zeta_{ANCOVA} = \frac{\hat{\alpha}_{Trt}}{SE(\hat{\alpha}_{Trt})}$ where $\hat{\alpha}_{Trt}$ is the MLE from the following ANCOVA model: $y_{ijT} = \alpha_0 + \alpha_{Trt} I(i = 1) + \alpha_u u_{ij} + \epsilon_{ij}$.

Simulation Results

Table 3: Simulation Results with Missing[a]

Data Model	Interaction	Statistics[b]	Hypothesis Test	Power[c]	Type I Error[c]
Full (CS)	Moderate	ζ_T	Last Time Point	0.193(0.328)	0.060(0.047)
		ζ_{ANCOVA}		0.285(0.327)	0.064(0.044)
		ζ_{FUN}		0.310(0.343)	0.049(0.049)
		ζ_{MSL}		0.989(0.987)	0.054(0.046)
		ζ_{LRT}	Overall Effect	0.968(0.965)	0.054(0.044)
		ζ_{MSA}		0.995(0.995)	0.054(0.046)

a: results based on 1000 simulations with 100 subjects at each treatment arm
b: model selection via BIC with 200 bootstrap resampling
c: values inside parentheses are based on no missing scenario
ζ_T: t-test for last time point effect
ζ_{ANCOVA}: test last time point effect via ANCOVA model
ζ_{FUN}: test last time point effect via full mixed effect model with UN covariance
ζ_{MSL}: model selection test statistics for testing last time point effect
ζ_{LRT}: mixed effects model based likelihood ratio test for overall effects
ζ_{MSA}: model selection statistics for testing overall effects

Simulation Results (Cont.)

Table 4: Simulation Results with Missing[a]

Data Model	Interaction	Statistics[b]	Hypothesis Test	Power[c]	Type I Error[c]
Main Effects (CS)	None	ζ_T	Last Time Point	0.176(0.325)	0.060(0.047)
		ζ_{ANCOVA}		0.265(0.331)	0.064(0.044)
		ζ_{FUN}		0.303(0.338)	0.049(0.049)
		ζ_{MSL}		0.689(0.710)	0.054(0.046)
		ζ_{LRT}	Overall Effect	0.463(0.486)	0.054(0.044)
		ζ_{MSA}		0.689(0.710)	0.054(0.046)

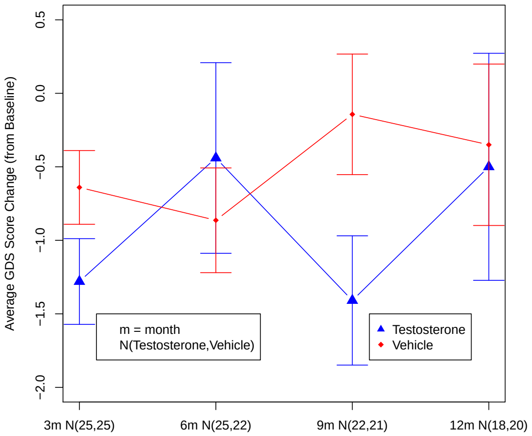
a: results based on 1000 simulations with 100 subjects at each treatment arm
b: model selection via BIC with 200 bootstrap resampling
c: values inside parentheses are based on no missing scenario
ζ_T: t-test for last time point effect
ζ_{ANCOVA}: test last time point effect via ANCOVA model
ζ_{FUN}: test last time point effect via full mixed effect model with UN covariance
ζ_{MSL}: model selection test statistics for testing last time point effect
ζ_{LRT}: mixed effects model based likelihood ratio test for overall effects
ζ_{MSA}: model selection statistics for testing overall effects

Real Application Example

- Testosterone's Cognitive Effect (Borst et. al. 2014)
  - 60 subjects
  - two treatment arms: testosterone vs vehicle
  - subject randomly assigned
  - outcome: geriatric depression scale (GDS: $0 \sim 30$)
  - higher score means more depressed
  - repeatedly measured at baseline, 3, 6, 9, and 12 months

Real Application Example (Cont.)

Figure 2: Average GDS Score Change (from Baseline) Comparison



Real Application Example (Cont.)

- time by treatment interaction strong but not significant (p-value=0.10)
- overall effects test by ζ_{LRT}: p-value=0.04
- overall effects test by ζ_{MSA}:
  - model selection $\Rightarrow$ optimal model = full model with unstructured covariance
  - p-value=0.04
- tested by ζ_T with last time point info only: p-value=0.87

Discussions

- Proposed statistics
  - make use of information from optimal model deemed for the data $\Rightarrow$ powerful for repeated measurement data.
  - utilize the information across each measurement time point $\Rightarrow$ more robust and flexible for missing data.
- Restricted cluster bootstrapping $\Rightarrow$ valid covariance estimate $\Rightarrow$ valid statistical inference.
- Extension to other data types deserves further investigations.

References

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THANK YOU