Analysis of longitudinal imaging data

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Introduction

The Sandwich Estimator method

An adjusted Sandwich Estimator method

Outline

1. Introduction
2. The Sandwich Estimator method
3. An adjusted Sandwich Estimator method
Example of longitudinal studies in neuroimaging

Example 1

Effect of drugs (morphine and alcohol) versus placebo over time on Resting State Networks in the brain (Khalili-Mahani et al, 2011)

- 12 subjects
- 21 scans/subject!!!
- Balanced design

Study design:
Example of longitudinal studies in neuroimaging

Example 2

fMRI study of longitudinal changes in a population of adolescents at risk for alcohol abuse

- 86 subjects
- 2 groups
- 1, 2, 3 or 4 scans/subjects (missing data)
- Total of 224 scans
- Very unbalanced design (no common time points for scans)
Why is it challenging to model longitudinal data in neuroimaging?

Longitudinal modeling is a standard biostatistical problem and standard solutions exist:

- **Gold standard: Linear Mixed Effects (LME) model**
  - Iterative method → generally slow and may fail to converge
  - E.g., 12 subjects, 8 visits, Toeplitz, LME with unstructured intra-visit correlation fails to converge 95 % of the time.
  - E.g., 12 subjects, 8 visits, CS, LME with random int. and random slope fails to converge 2 % of the time.

- **LME model with a random intercept per subject**
  - May be slow (iterative method) and only valid with Compound Symmetric (CS) intra-visit correlation structure

- **Naive-OLS (N-OLS) model which include subject indicator variables as covariates**
  - Fast, but only valid with CS intra-visit correlation structure
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3. An adjusted Sandwich Estimator method
The Sandwich Estimator (SwE) method

- Use of a simple OLS model (without subject indicator variables)
- The fixed effects parameters $\beta$ are estimated by

$$\hat{\beta}_{OLS} = \left( \sum_{i=1}^{M} X'_i X_i \right)^{-1} \sum_{i=1}^{M} X'_i y_i$$

- The fixed effects parameters covariance $\text{var}(\hat{\beta}_{OLS})$ are estimated by

$$\text{SwE} = \left( \sum_{i=1}^{M} X'_i X_i \right)^{-1} \left( \sum_{i=1}^{M} X'_i \hat{V}_i X_i \right) \left( \sum_{i=1}^{M} X'_i X_i \right)^{-1}$$

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Property of the Sandwich Estimator (SwE)

\[ \text{SwE} = \left( \sum_{i=1}^{M} X'_i X_i \right)^{-1} \left( \sum_{i=1}^{M} X'_i \hat{V}_i X_i \right) \left( \sum_{i=1}^{M} X'_i X_i \right)^{-1} \]

If \( V_i \) are consistently estimated, the SwE tends asymptotically (Large samples assumption) towards the true variance \( \text{var}(\hat{\beta}_{OLS}) \). (Eicker, 1963; Eicker, 1967; Huber, 1967; White, 1980)
In practice, $V_i$ is generally estimated from the residuals $r_i = y_i - X_i\hat{\beta}$ by

$$\hat{V}_i = r_i r'_i$$

and the SwE becomes

$$\text{Het. HC0 SwE} = \left( \sum_{i=1}^{M} X'_i X_i \right)^{-1} \left( \sum_{i=1}^{M} X'_i r_i r'_i X_i \right) \left( \sum_{i=1}^{M} X'_i X_i \right)^{-1}$$
Simulations: setup

- Monte Carlo Gaussian null simulation (10,000 realizations)
- For each realization,
  1. Generation of longitudinal Gaussian null data (no effect) with a CS or a Toeplitz intra-visit correlation structure:

  **Compound Symmetric**
  \[
  \begin{pmatrix}
  1 & 0.8 & 0.8 & 0.8 & 0.8 \\
  0.8 & 1 & 0.8 & 0.8 & 0.8 \\
  0.8 & 0.8 & 1 & 0.8 & 0.8 \\
  0.8 & 0.8 & 0.8 & 1 & 0.8 \\
  0.8 & 0.8 & 0.8 & 0.8 & 1 \\
  \end{pmatrix}
  \]

  **Toeplitz**
  \[
  \begin{pmatrix}
  1 & 0.8 & 0.6 & 0.4 & 0.2 \\
  0.8 & 1 & 0.8 & 0.6 & 0.4 \\
  0.6 & 0.8 & 1 & 0.8 & 0.6 \\
  0.4 & 0.6 & 0.8 & 1 & 0.8 \\
  0.2 & 0.4 & 0.6 & 0.8 & 1 \\
  \end{pmatrix}
  \]
  2. Statistical test (F-test at $\alpha$) on the parameters of interest using each different methods (N-OLS, LME and SWE) and recording if the method detects a (False Positive) effect

- For each method, rel. FPR $= \frac{\text{Number of False Positive}}{10,000\alpha}$
Simulations: LME vs N-OLS vs Het. HC0 SwE

Linear effect of visits
Group 2 versus group 1
Compound symmetry
8 vis., F(1,N−p) at 0.05

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Bias adjustments: the Het. HC2 SWe

In an OLS model, we have

\[(I - H)\text{var}(y)(I - H) = \text{var}(r)\]

where \(H = X(X'X)^{-1}X'\)

Under independent homoscedastic errors,

\[(I - H)\sigma^2 = \text{var}(r)\]
\[(1 - h_{ik})\sigma^2 = \text{var}(r_{ik})\]

\[\sigma^2 = \text{var}\left(\frac{r_{ik}}{\sqrt{1 - h_{ik}}}\right)\]

This suggests to estimate \(V_i\) by

\[\hat{V}_i = r_{i}^* r_{i}^{*'} \text{ where } r_{i}^* = \frac{r_{ik}}{\sqrt{1 - h_{ik}}}\]
Bias adjustments: the Het. HC2 SWe

Using in the SwE

\[ \hat{V}_i = r_{i}^* r_{i}^* \] where \( r_{i}^* = \frac{r_{ik}}{\sqrt{1 - h_{ik}}} \)

We obtain

\[
\text{Het. HC2 SwE} = \left( \sum_{i=1}^{M} X'_i X_i \right)^{-1} \left( \sum_{i=1}^{M} X'_i r_{i}^* r_{i}^* X_i \right) \left( \sum_{i=1}^{M} X'_i X_i \right)^{-1}
\]
Homogeneous SwE

In the standard SwE, each $V_i$ is normally estimated from only the residuals of subject $i$. It is reasonable to assume a common covariance matrix $V_0$ for all the subjects and then, we have

$$
\hat{V}_{0kk'} = \frac{1}{N_{kk'}} \sum_{i=1}^{N_{kk'}} r_{ik} r_{ik'}
$$

$\hat{V}_{0kk'}$: element of $\hat{V}_0$ corresponding to the visits $k$ and $k'$

$N_{kk'}$: number of subjects with both visits $k$ and $k'$

$r_{ik}$: residual corresponding to subject $i$ and visit $k$

$r_{ik'}$: residual corresponding to subject $i$ and visit $k'$

$$
\hat{V}_i = f(\hat{V}_0)
$$
Null distribution of the test statistics with the SwE

- $H_0 : L\hat{\beta} = 0$, $H_1 : L\hat{\beta} \neq 0$
- $L$: contrast matrix of rank $q$

Using multivariate statistics theory, we can derive the test statistic

$$\frac{M - p_B - q + 1}{(M - p_B)q} (L\hat{\beta})' (LSwEL')^{-1} (L\hat{\beta}) \sim F(q, M - p_B - q + 1)$$

$q=1$, the test becomes

$$(L\hat{\beta})' (LSwEL')^{-1} (L\hat{\beta}) \sim F(1, M - p_B) \neq F(1, N - p)$$
Simulations: LME vs N-OLS vs unadjusted SwE

- Linear effect of visits
- Group 2 versus group 1
- Compound symmetry
- 8 vis., F(1,N−p) at 0.05

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Number of subjects
Relative FPR (%)
12 50 100 200
0 100 200 300 400 500 600 700

Het. HC0 SwE
N−OLS
LME
Simulations: unadjusted SwE vs adjusted SwE

- Linear effect of visits
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Simulation with real design
Example 2

![Graph](image)
Simulation with real design

Example 2

Scans index vs. relative Age
Real design

Compound Symmetry
F(1, M−2) at 0.05 for Hom. HC2
OTW F(1, N−p) at 0.05

Relative FPR (%)
Real design

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Real design

Toeplitz

F(1,M−2) at 0.05 for Hom. HC2

OTW F(1,N−p) at 0.05

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Future works

- Assessment of the SwE method within the context of multiple testing (Does the RFT work with the SwE method?)
  - Probably need to use a spatial regularization
  - Will be checked with the plug-in for SPM (currently in progress)
- Assessment of the SwE method with real images
  - Will be done with the plug-in for SPM (currently in progress)
Summary

- Longitudinal standard methods are not really appropriate to Neuroimaging, particularly when Compound Symmetry does not hold
- The SwE method
  - Accurate in a large range of settings
  - Easy to specify
  - No iteration needed
    - Quite fast
    - No convergence issues
  - But, adjustments essential in small samples
  - But, assessment needed within the context of multiple testing
Thanks for your attention!