Fast and accurate modelling of longitudinal neuroimaging data

B. Guillaume$^{124}$  L. Waldorp$^3$  T. Nichols$^1$

$^1$Department of Statistics
University of Warwick

$^2$Cyclotron Research center
University of Liège

$^3$Department of Psychological Methods
University of Amsterdam

$^4$GlaxoSmithKline

OHBM, 2012
An example of a longitudinal study in brainimaging

fMRI study of longitudinal changes in a population of adolescents at risk for alcohol abuse linked to Heitzeg et al. (2010)

- 86 subjects
- 2 groups (Low risk: 47 subj. and High risk: 39 subj.)
- Missing data (1, 2, 3 or 4 scans/subject)
- Go/No-go task
- No common time points

2nd-level standard modelling in SPM
An example of a longitudinal study in brainimaging

fMRI study of longitudinal changes in a population of adolescents at risk for alcohol abuse linked to Heitzeg et al. (2010)

- 86 subjects
- 2 groups (Low risk: 47 subj. and High risk: 39 subj.)
- Missing data (1, 2, 3 or 4 scans/subject)
- Go/No-go task
- No common time points

2nd-level standard modelling in SPM
An example of a longitudinal study in brainimaging

fMRI study of longitudinal changes in a population of adolescents at risk for alcohol abuse linked to Heitzeg et al. (2010)

- 86 subjects
- 2 groups (Low risk: 47 subj. and High risk: 39 subj.)
- Missing data (1, 2, 3 or 4 scans/subject)
- Go/No-go task
- No common time points

2nd-level standard modelling in SPM

Only valid under **Compound Symmetry**:

\[
\text{var}(y_i) = \sigma^2 \begin{pmatrix}
1 & \rho & \cdots & \rho \\
\rho & 1 & \cdots & \rho \\
\vdots & \vdots & \ddots & \vdots \\
\rho & \rho & \cdots & 1
\end{pmatrix}
\]
Is there an alternative method?

- Gold standard method for longitudinal data in Biostatistics: Linear Mixed Effects (LME) modelling (Laird and Ware, 1982):

\[ y_i = X_i \beta \underbrace{+ Z_i b_i}_{\text{Fixed effects Random effects}} + e_i \]

- Unfortunately, LME has drawbacks:
  - Random effects not easy to specify
  - Use of iterative algorithms
    - generally slow
    - may fail to converge to a solution:
      E.g., 12 subjects, 8 visits, Toeplitz (linearly decaying) correlation struct., LME with unstructured intra-visit correlation fails to converge 95% of the time.
      E.g., 12 subjects, 8 visits, Compound Symmetry, LME with random int. and random slope fails to converge 2% of the time.
The Sandwich Estimator (SwE) method

- Marginal OLS modelling used:

\[
y_i = X_i \beta + \beta_{oi} + e_i
\]

- Fixed effects
- Subject indicator covariates

- \(\beta\) estimated by OLS estimate \(\hat{\beta}_{OLS}\)
- \(\text{var}(\hat{\beta}_{OLS})\) estimated by the Sandwich Estimator (Eicker, 1963):

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

\[\text{Bread} \quad \text{Meat} \quad \text{Bread}\]

with \(\hat{V}_i = r_i r_i'\) and \(r_i = y_i - X_i \hat{\beta}\)
The adjusted Sandwich Estimator (SwE) method

- **SwE property:**

\[
\lim_{M \to +\infty} \text{SwE} = \text{var}(\hat{\beta}_{OLS})
\]

→ **Large sample assumption**

- In order to enhance the accuracy of the SwE method in **small samples**, we propose to use:
  - Small sample bias adjustment (MacKinnon and White, 1985)
  - Small sample distributional adjustment of the statistical test Null distribution (Waldorp, 2009)
  - Assumption of a common covariance matrix among subjects
Assessment method

- Methods accuracy assessed by Null Gaussian Monte Carlo simulations (10,000 realizations)
- Metric used:

  \[
  \text{Relative False Positive Rate (rel. FPR)} = \frac{\mathbb{E}(\text{FPR}_{\text{Method}})}{\text{Nominal FPR}}
  \]

- 2 correlation structures tested:

  **Compound Symmetry**
  
  E.g., for subject 1:

  \[
  \begin{pmatrix}
  1 & 0.8 & 0.8 & 0.8 \\
  0.8 & 1 & 0.8 & 0.8 \\
  0.8 & 0.8 & 1 & 0.8 \\
  0.8 & 0.8 & 0.8 & 1
  \end{pmatrix}
  \]

  **Non Compound Symmetry**
  
  E.g., for subject 1:

  \[
  \begin{pmatrix}
  1 & 0.7 & 0.51 & 0.31 \\
  0.7 & 1 & 0.81 & 0.61 \\
  0.51 & 0.81 & 1 & 0.8 \\
  0.31 & 0.61 & 0.8 & 1
  \end{pmatrix}
  \]
Simulation results

- F-test at 0.05 as level of significance

### Compound Symmetry
Constant intra–visit correlation of 0.8

- Mean effect
  - High vs. Low
- Linear effect of age
  - High vs. Low
- Quadratic effect of age
  - High vs. Low

N - OLS (SPM)
- LME with random int.
- Unadjusted SwE
- Adjusted SwE

Relative FPR (%)

- 1079%

### Non Compound Symmetry
Linear decay of the intra–visit correlation of 0.1/year

- Mean effect
  - High vs. Low
- Linear effect of age
  - High vs. Low
- Quadratic effect of age
  - High vs. Low

N - OLS (SPM)
- LME with random int.
- Unadjusted SwE
- Adjusted SwE

Relative FPR (%)

- 954%
Summary

- Longitudinal standard methods not really appropriate to neuroimaging data:
  - LME
    - Difficult to specify
    - Generally slow
    - Convergence issues
  - N-OLS
    - Issues when Compound Symmetry does not hold
    - Cannot accommodate pure between covariates (e.g., gender)
- The SwE method, particularly with small samples adjustments,
  - Accurate in a large range of settings
  - Easy to specify
  - No iteration needed
    - Quite fast
    - No convergence issues
  - Can accommodate pure between covariates (e.g., gender)
Acknowledgment

- Data
  - M. Heitzeg

- Funding
  - GlaxoSmithKline through the Marie Curie Initial Training Network "Neurophysics"