SwE-Toolbox: Fast and accurate modelling of longitudinal neuroimaging data

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Dependent Data in Neuroimaging

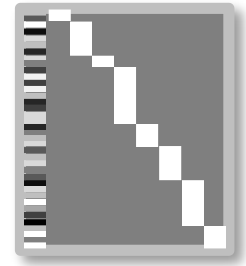
- More and more studies have dependent data
  - Longitudinal data with ≥ 3 visits, imbalance
  - Repeated measures, e.g. ≥ 2 contrasts at 2nd level
  - Heritability twin/family studies

ADNI Subject Counts by Visit

	AD	MCI	NC	Total
0 Mo	188	400	229	817
6 Mo	159	346	208	713
12 Mo	138	326	196	660
18 Mo	0	286	0	286
24 Mo	105	244	172	521
36 Mo	0	170	147	317

Dependent Data in Neuroimaging: Current Methods

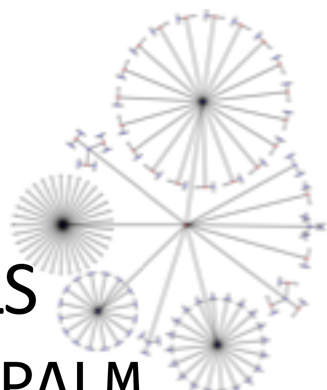
Naïve OLS
Design Matrix



Compound Symmetric
Correlation

	0.2	0.2	0.2
0.2		0.2	0.2
0.2	0.2		0.2
0.2	0.2	0.2	

- '**Naïve OLS**' - just add subject dummies
  - Only valid for balanced design & compound symmetry (CS)
  - FSL: FEAT can account for 1st level variance, making this '**Naïve WLS**'
  - SPM: Accounts for dependence, but one model for whole brain, giving a '**Global GLS**'
- Permutation w/ PALM
  - Accounts for dependence structure
  - But no CI's/SE's, just P-values, as model is OLS
  - `http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PALM`



Dependent Data in Neuroimaging: Non-Imaging Approach

- Best practice: Linear Mixed Effects
  - Bread & butter biostatistics problem
    - Optimise mixed effects likelihood
    - R's lme & lmer, SAS's proc_mixed
  - But these "Gold standards" are slow & unreliable
  - Simulation: R's lme with 12 subjects, 8 visits, &...
    - Toeplitz truth, unstructured correlation model
      95% convergence failure rate!
    - CS truth, random intercept & slope model
      2% convergence failure rate!
      - Not so bad, but 2,000 NaN voxels in a 100k brain!

ADNI Example: Longitudinal TBM

- 6 visits, highly imbalanced
- Naïve OLS model
  - Cannot have between-subject covariates
    - e.g. Age, gender
  - Questionable validity
    - Unbalanced design!
    - Compound symmetry?
      - Over 3 years?
      - With uneven sampling?
        - » 0/6/12/18/24 -> 36

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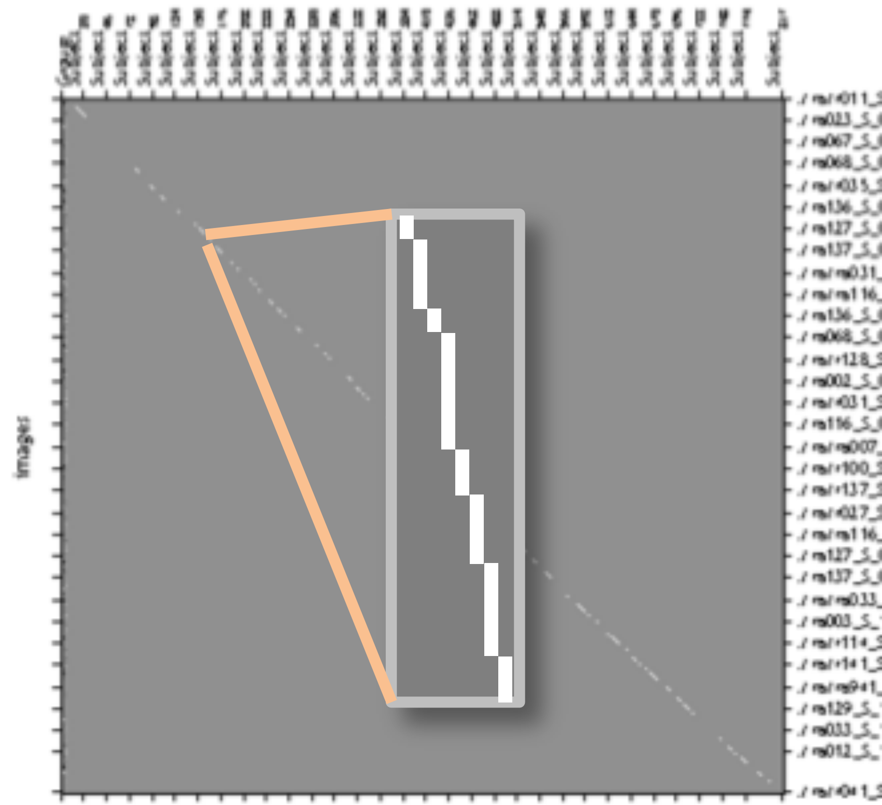
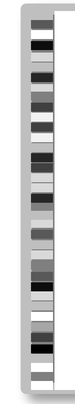


Sandwich Estimator

Marginal Model



- OLS "Marginal model" (no subject dummies)

$$y_i = \underbrace{X_i\beta}_{\text{Fixed effects}} + \cancel{\underbrace{\beta_{0i}}_{\text{Family indicator covariates}}} + e_i$$

- Estimate arbitrary intra-subject correlation
- Adjust variance estimate of $\hat{\beta}_{OLS}$
  - ▶ var($\hat{\beta}_{OLS}$) estimated by the Sandwich Estimator (Eicker,1963):

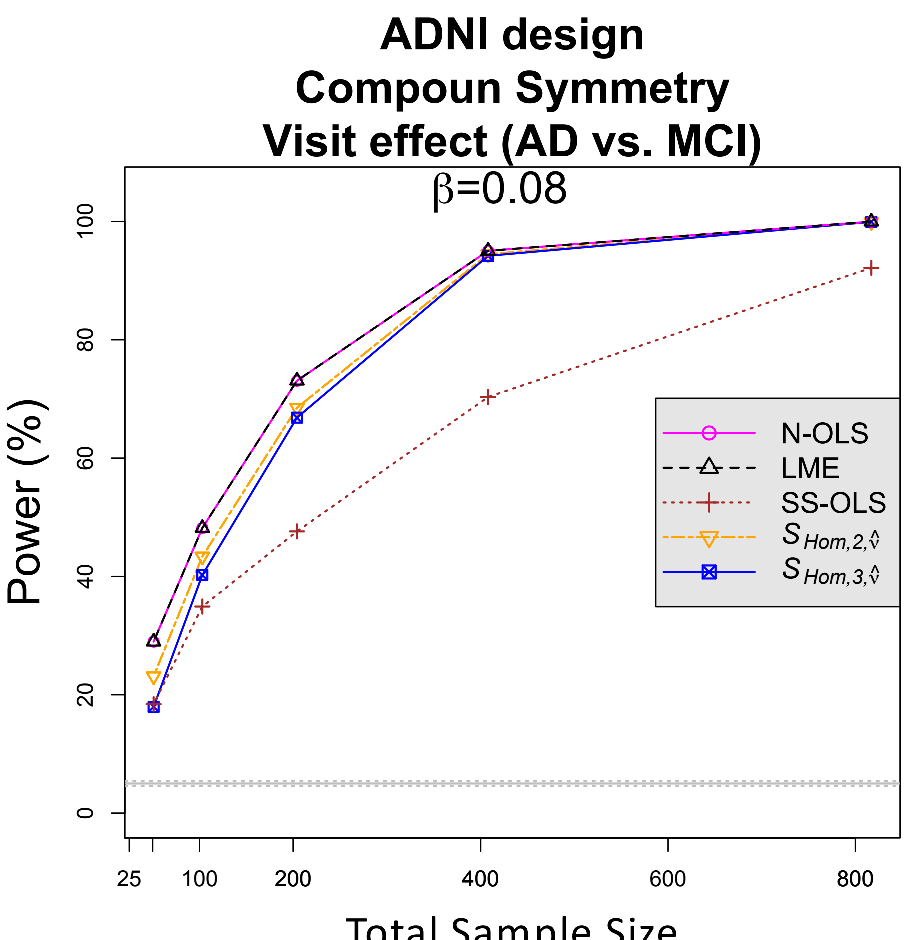
$$\text{SwE} = \underbrace{\left(\sum_{i=1}^{M} X_i' X_i\right)^{-1}}_{Bread} \underbrace{\left(\sum_{i=1}^{M} X_i' \hat{V}_i X_i\right)}_{Meat} \underbrace{\left(\sum_{i=1}^{M} X_i' X_i\right)^{-1}}_{Bread}$$

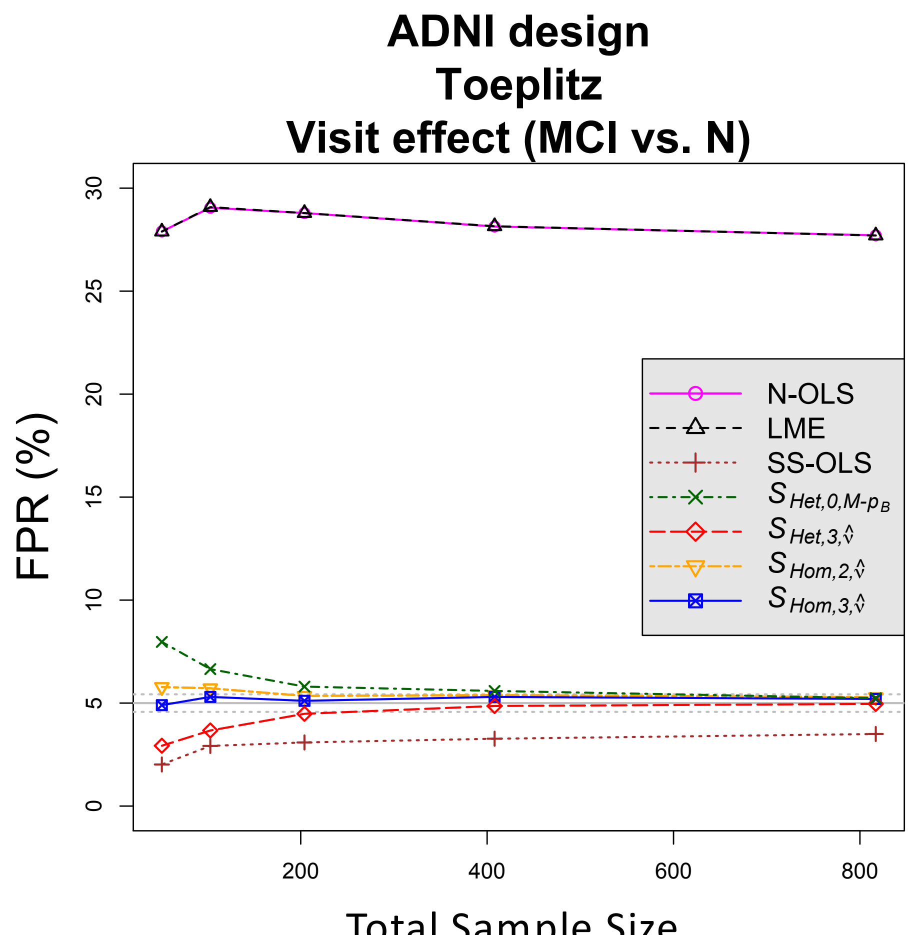
$$\text{with} \quad \hat{V}_i = r_i r_i' \quad \text{and} \quad r_i = y_i - X_i\hat{\beta}$$

  - Asymptotic method!
  - But we identified special sauce of small sample performance
    - Residuals (r_i) studentization *and* pooling V_i over subjects

Sandwich Simulations: Imbalanced Design

- Compound symmetry (CS), homogeneous variance
  - SwE nearly as powerful as LME
  - N-OLS has OK FPR (not shown)
- Without CS
  - N-OLS has catastrophic FPR
    - Even worse with het. var. over groups (not shown)

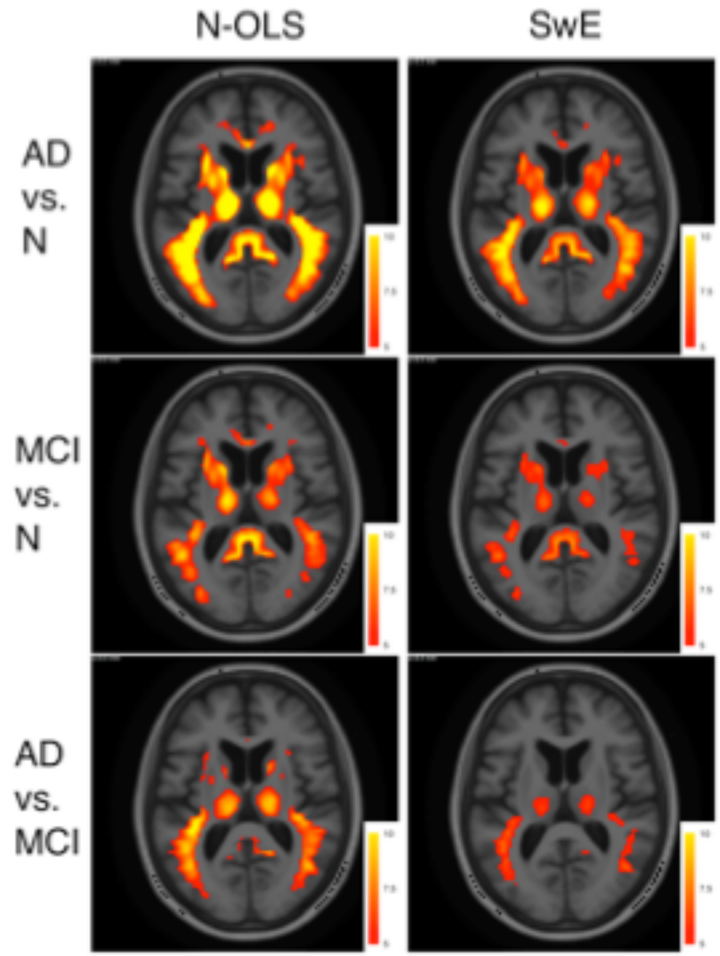




ADNI Real Data Analysis

- Model
  a. {N, MCI, AD} Intercept — Between Subj.
  b. Cross-sectional age — Between Subj.
     - Average age of each subject, centered
  c. Visit — Within Subj
     - Intrasubject centered age
  d. "Acceleration" — Btwn & Within Subj
     - Product of b & c
- Results (1)

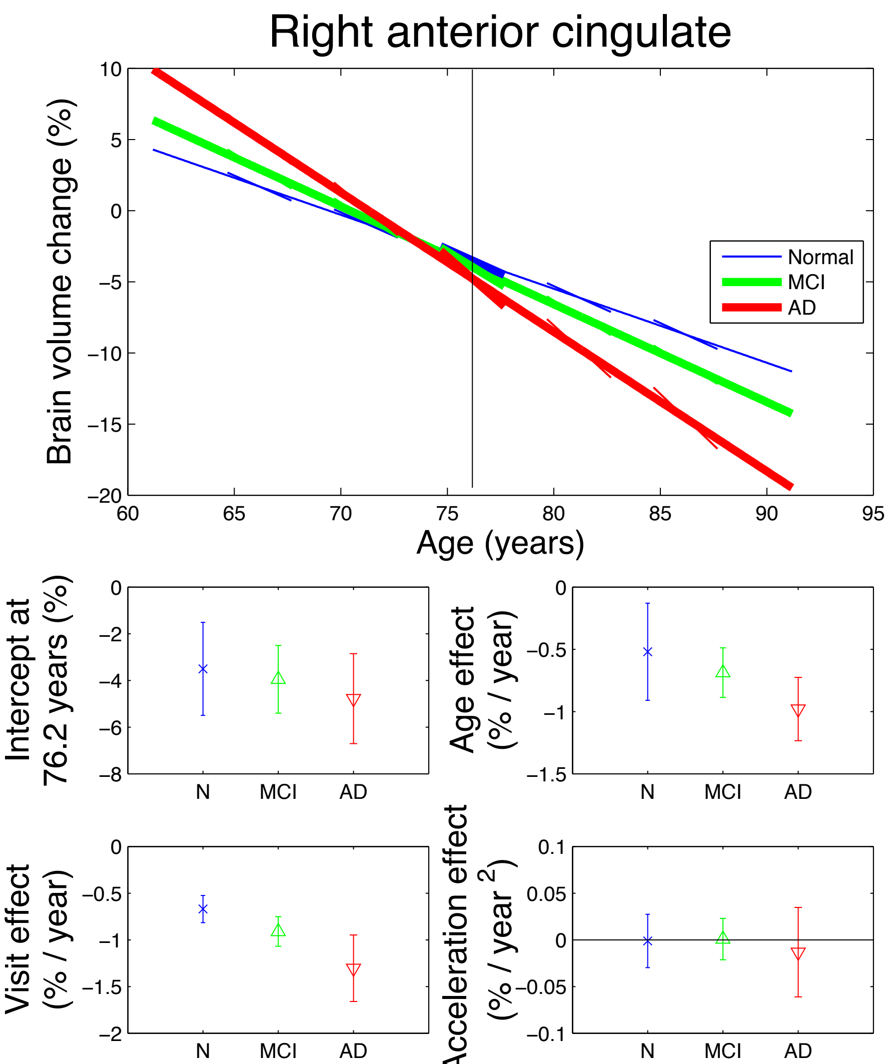
Main Group Contrasts, $T \geq 5$

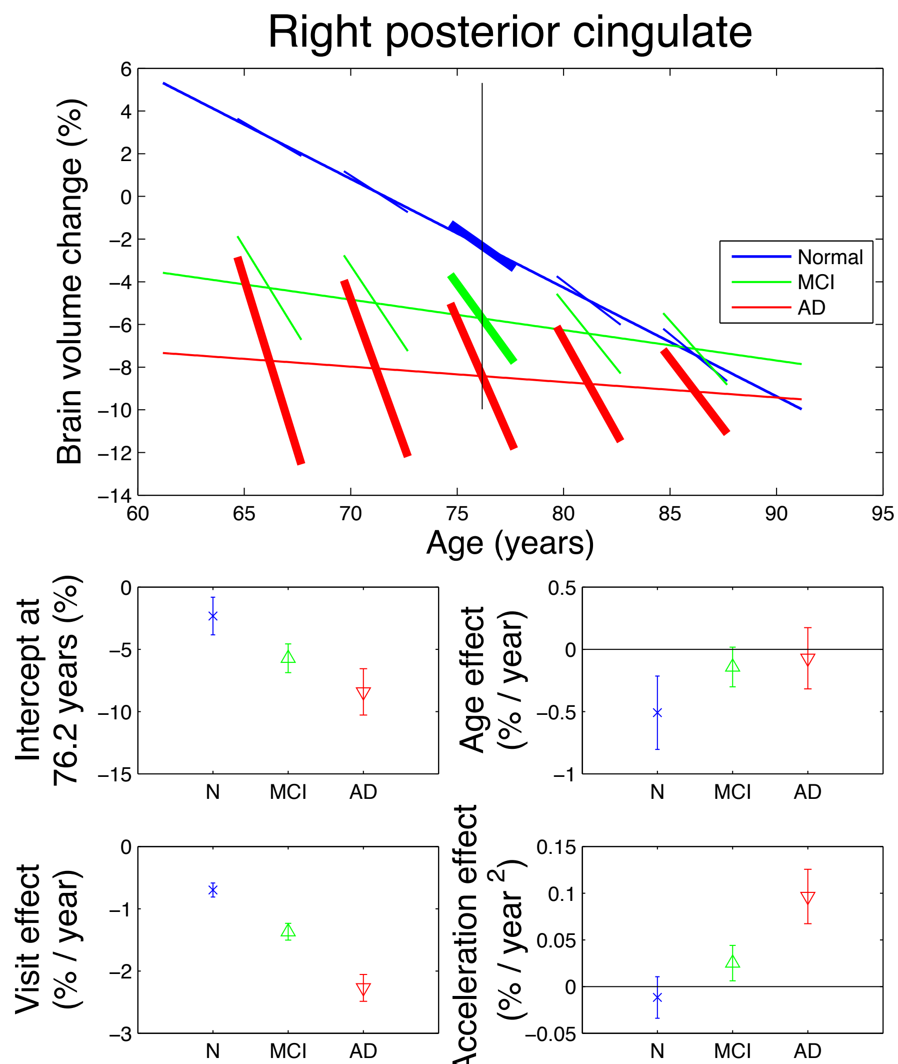


- N-OLS appears way more powerful, but power difference should be subtle
- N-OLS significance likely inflated due to non-CS correlation

Results (2): “Acceleration”

- Generally, cross-sectional and longitudinal change similar
- In atrophic areas: MCI & AD Deceleration!
  - Cohort effects most likely cause

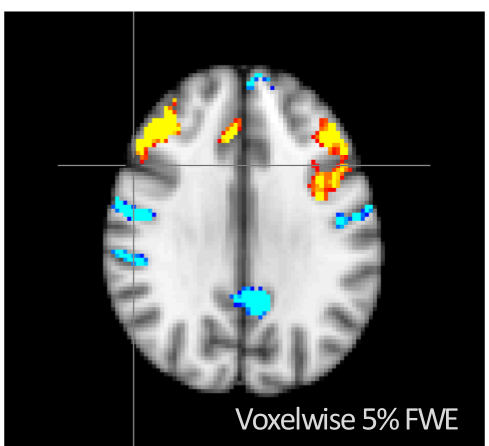


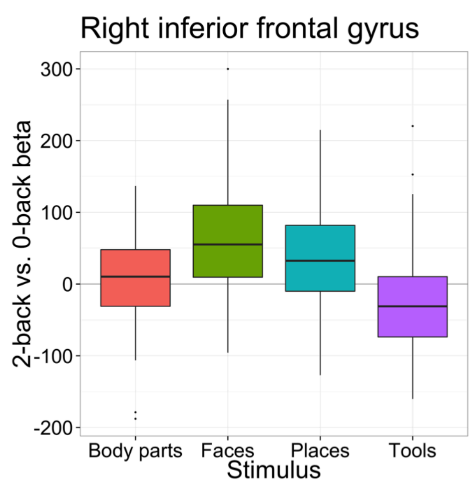


HCP Repeated Measures Example

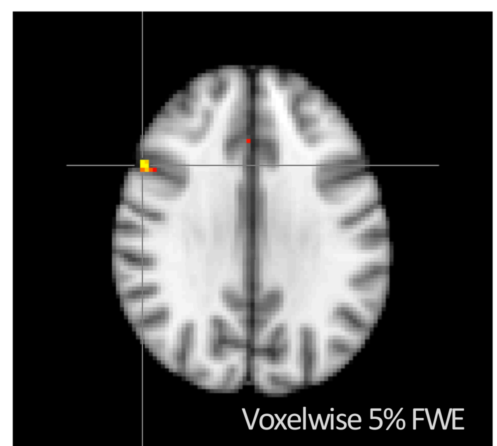
- HCP N-Back
  - 4 versions: body parts, faces, places and tools
  - 80 unrelated subjects, 3 contrasts:
    - 1) Avg +ve, 2) Avg –ve, 3) F-test for any diffs among the 4
    - F-test depends on accurate repeated measures variance
  - Interaction finds areas with no main effect

Main Effect
Avg +ve, -ve





Interaction
(Any diffs)

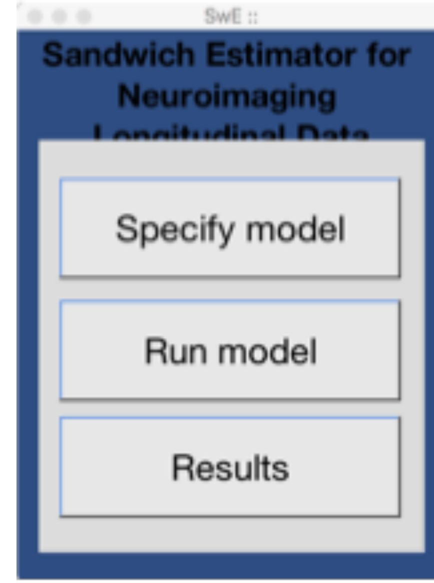


Longitudinal & Repeated Measures Neuroimaging Modelling

- Sandwich Estimator redux
  - Fit OLS marginal model
  - Estimate intrasubject (or intra-family) correlation
  - Compute StdErr's with "sandwich estimator", T's & P's
- Fast, flexible, reliable mixed effects inference

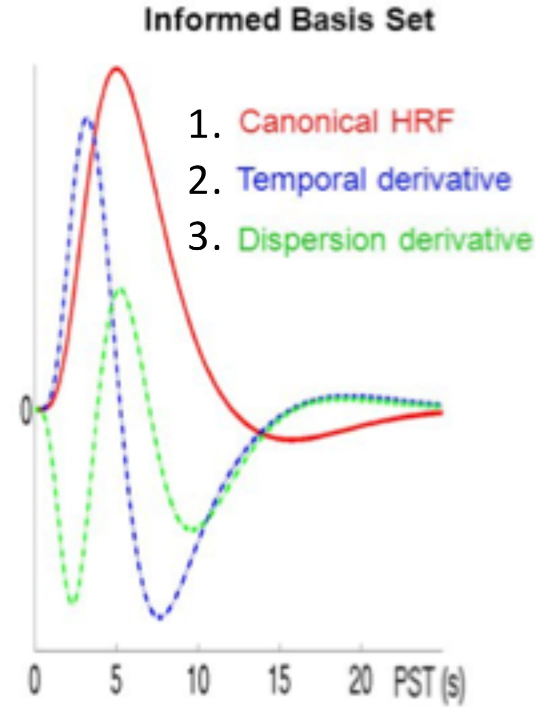
  Guillaume, Hua, Thompson, Waldorp, Nichols. (2014). Fast and accurate modelling of longitudinal and repeated measures neuroimaging data. *NeuroImage*, 94, 287–302.
- Matlab SwE Toolbox available
  - http://www.nisox.org/Software/SwE
- FSL SwE Toolbox in beta testing

Running SwE



- Launch: `swe`
  - (Need to add SwE to Matlab path)
- Specify model
  - SwE Type: “Modified”
    - Pool covariance estimates over subjects, w/in group
    - Subjects, Groups & Visits must be specified
  - SwE Type: “Classic”
    - No pooling
    - Only subjects specified

SPM Example: Henson Faces fMRI



- 12 subjects
- 3 contrasts / subject
  - "Informed HRF"
- Want to test for "any" effect
  - H_0: $\beta_1 = \beta_2 = \beta_3 = 0$
  - H_1: $\beta_1 \neq 0$ or $\beta_2 \neq 0$ or $\beta_3 \neq 0$
- SPM can do this *but* assumes common 3x3 covariance (scaled locally) for whole brain