Beyond Univariate Analyses: Multivariate Modeling of Functional Neuroimaging Data

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How Not to Analyze Your Data: A Skeptical Introduction to Modeling Methods
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Outline

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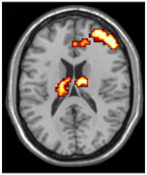
The Problem

Neuroactivation Studies

- Task-related designs
- Seek group-level inferences relating stimuli to neural response
  - Contrasts specify task-related changes (and possibly group differences) in neural activity
  - Estimation and hypothesis testing about group-level contrasts
- Multiple contrasts for each subject, derived from multiple tasks/effects
- Linear model framework (linear in parameters)



Univariate versus Multivariate Linear Models

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Univariate Linear Models

- Involve a single dependent variable
- May involve one or more independent variables
    - Multiple regression

Multivariate Linear Models

- Involve multiple dependent variables
- Dependent variables are possibly correlated
    - Over voxels
    - Over time
    - Related stimuli/tasks
- May involve one or more independent variables

Common Univariate Analysis Framework

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Two-stage Model: Mass Univariate Approach

- First, fit a linear model separately for each subject (at each voxel)
  - Convolution with a HRF
  - Temporal correlations between scans: AR models (+ white noise)
    - Linear covariance structure
    - Pre-coloring/temporal smoothing [Worsley and Friston, 1995]
    - Pre-whitening [Bullmore et al, 1996; Purdon and Weisskoff, 1998]
    - Alternative structures available for PET [Bowman and Kilts, 2003]
- Second, fit linear model that combines subject-specific estimates
  - A two-stage (random effects) model
    - Simplifies computations*
    - Sacrifices efficiency
- For Inference: Compute t-statistics at each voxel and threshold
  - Consider a multiple testing adjustment (Bonferonni-type, FDR, RFT)

Common Univariate Analysis Framework

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Properties

- Two-stage (random effects) model
  - Simplifies computations
  - Sacrifices efficiency
- May assume independence between different regression coefficients
- Assumes independence between different brain locations

Data Example

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Working Memory in Schizophrenia Patients

- N=28 subjects: 15 schizophrenia patients and 13 healthy controls
- fMRI Tasks: Serial Item Recognition Paradigm (SIRP)
  - Encoding set: Memorize 1, 3, or 5 target digits.
  - Probing set: Shown single digit probes and asked to press a button:
    - with their index finger, if the probe matched
    - with their middle finger, if not.
  - Between conditions, subjects fixated on a flashing cross.
- 6 runs per subject: (177 scans per run for each subject)
  - 3 runs of working memory tasks on each of 2 days
- Objective: Compare working memory-related brain activity between patients and controls

Data from the Biomedical Informatics Research Network (BIRN) [1]: Potkin et al. (2002).

Statistical Modeling

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General Linear Model: Stage I

$$\mathbf{Y}_i(v) = \mathbf{X}_{iv}\beta_i(v) + \mathbf{H}_{iv}\gamma_i(v) + \varepsilon_i(v)$$

$\mathbf{Y}_i(v)$	$S \times 1$	serial BOLD activity at voxel v.
$\mathbf{X}_{iv}$	$S \times q$	design matrix reflecting fixation and WM tasks.
$\beta_i(v)$	$q \times 1$	parameter vector linking experimental tasks.
$\varepsilon_i(v)$	$S \times 1$	random error about ith subject's mean.
$\mathbf{H}_{iv}$	$S \times m$	contains other covariates, e.g. high-pass filtering.
$\varepsilon_i(v)$	$\sim$	$\text{Normal}(\mathbf{0}, \tau_v^2\mathbf{V})$.

Statistical Modeling: Univariate

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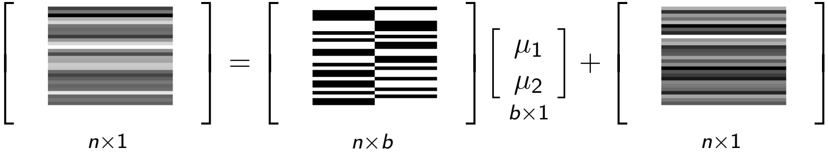
General Linear Model: Stage II (Contrast of Interest)

$$\mathbf{C}\boldsymbol{\beta}_{ij}(v) = \mu_j(v) + e_{ij}(v)$$

$\boldsymbol{\beta}_{ij}(v)$		stage I fixation and WM parameters; subject i, group j.
$\mathbf{C}$		contrast matrix (linear combinations of elements in $\boldsymbol{\beta}_{ij}(v)$).
$\mu_j(v)$		group-level mean (for group j).
$e_{ij}(v)$		random error.
$e_{ij}(v)$	$\sim$	Normal$(\mathbf{0}, \sigma^2(v))$.

Statistical Modeling: Univariate

Working Memory Data:



General Linear Model: Stage II (Matrix Model)

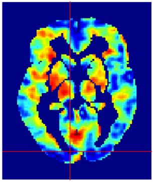
$$\begin{bmatrix} \mathbf{C}\beta_{11}(v) \\ \vdots \\ \mathbf{C}\beta_{n_c1}(v) \\ \mathbf{C}\beta_{12}(v) \\ \vdots \\ \mathbf{C}\beta_{n_p2}(v) \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ \vdots & \vdots \\ 1 & 0 \\ 0 & 1 \\ \vdots & \vdots \\ 0 & 1 \end{bmatrix} \begin{bmatrix} \mu_1(v) \\ \mu_2(v) \end{bmatrix} + \begin{bmatrix} e_{11}(v) \\ \vdots \\ e_{n_c1}(v) \\ e_{12}(v) \\ \vdots \\ e_{n_p2}(v) \end{bmatrix}$$

$$(\mathbf{I} \otimes \mathbf{C})\beta(v) = \mathbf{X}\mu(v) + \mathbf{e}(v)$$

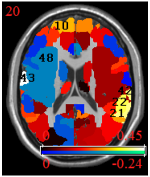
Statistical Modeling

Mass Univariate Approach

- May not fully acknowledge the correlations between
  - Multiple effects/contrasts
  - Effects/contrasts at different voxels



- Separately models contrasts of interest
  - Does not yield information on correlations between contrasts.
  - Does not enable comparisons or linear combinations of contrasts.



Statistical Modeling

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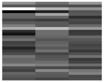
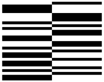
Working Memory Data:



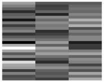
$n \times p$

$=$



$n \times q$

$$\begin{bmatrix} \mu_{11} & \mu_{12} & \mu_{13} \\ \mu_{21} & \mu_{22} & \mu_{23} \end{bmatrix}_{q \times p} +$$



$n \times p$

General Linear Multivariate Model: Stage II

$$\boldsymbol{\beta}(v) = \mathbf{X}\boldsymbol{\mu}(v) + \mathbf{e}(v)$$

- Multiple summary statistics (or contrasts) included for each subject
  - E.g. working memory load contrasts
- Rows contain data from different subjects
  - Each row assumed to have variance covariance matrix $\boldsymbol{\Sigma}$ reflecting correlations between summary statistics/contrasts
- Define $\theta(v) = \mathbf{C}\boldsymbol{\mu}(v)\mathbf{U}$, e.g. $(\mu_{13} - \mu_{11}) - (\mu_{23} - \mu_{21})$.

Statistical Modeling

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Contrast Variance:

- Define $\theta(v) = \mathbf{C}\boldsymbol{\mu}(v)\mathbf{U}$, e.g. $(\mu_{13} - \mu_{11}) - (\mu_{23} - \mu_{21})$
  - $\mathbf{C} = \begin{bmatrix} 1 & -1 \end{bmatrix}$
  - $\mathbf{U} = \begin{bmatrix} -1 \\ 0 \\ 1 \end{bmatrix}$

$\mathrm{Var}(\hat{\theta})$

$$\begin{aligned}
\mathrm{Var}(\hat{\theta}(v)) &= \mathrm{Var}(\hat{\theta}(v)') \\
&= \mathrm{Var}\left[\mathrm{vec}((\mathbf{C}\hat{\boldsymbol{\mu}}(v)\mathbf{U})')\right] \\
&= \mathbf{C}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{C}' \otimes \mathbf{U}'\boldsymbol{\Sigma}(v)\mathbf{U} \\
&= \left(\frac{1}{n_c} + \frac{1}{n_p}\right)(\sigma_1^2 + \sigma_3^2 - 2\sigma_{13}), \text{ for WM data.}
\end{aligned}$$

Application to Working Memory Data

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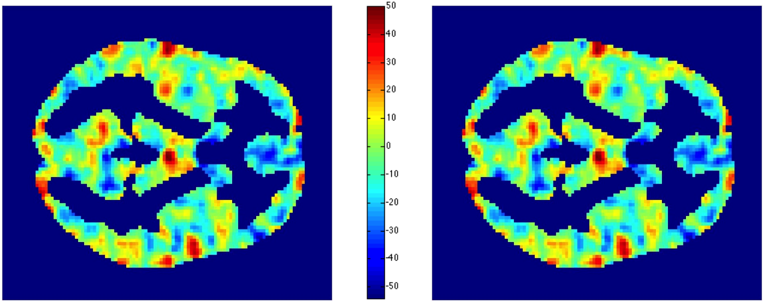
- Stage I analysis produces estimates of visual fixation, WM load 1, WM load 3, and WM load 5 for each subject (FSL, SPM, etc).
- Compute contrasts of each WM load versus fixation for each subject.
  - (1) Load 1 vs. Fixation, (2) Load 3 vs. Fixation, and (3) Load 5 vs. Fixation.
- Fit second-stage univariate model (GLM) to estimate the group-level effects and associated variances.
  - Estimate final contrast to compare Load 3 vs Load 1 between controls and schizophrenia patients
  - Calculate test-statistic
- Fit second-stage multivariate model to estimate the group-level effects and associated variances.
  - Estimate final contrast to compare Load 3 vs Load 1 between controls and schizophrenia patients
  - Calculate test-statistic

Estimation

Contrast estimates:

GLMM	GLUM

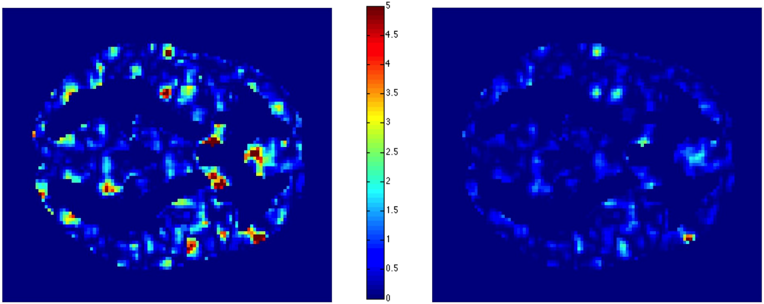


- Both methods produce unbiased estimates of regression coefficients and associated contrasts.
- $\theta = [\text{task3} - \text{task1}]_{\text{Controls}} - [\text{task3} - \text{task1}]_{\text{Patients}}$

Test Statistics

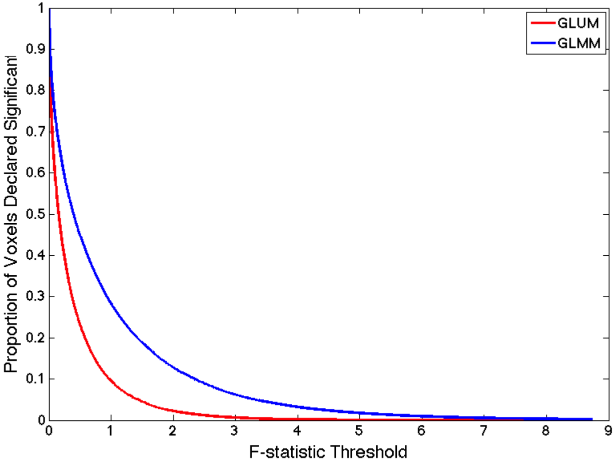
F-statistics:

GLMM	GLUM



- The GLMM often produces larger test statistics than the GLUM.
- $\theta = [\text{task3} - \text{task1}]_{\text{Controls}} - [\text{task3} - \text{task1}]_{\text{Patients}}$

Test Statistics

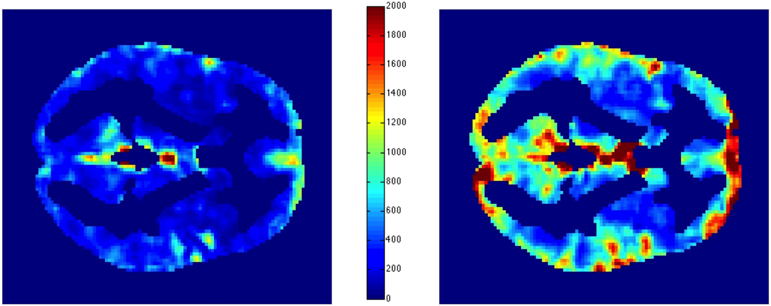


- This figure clearly reveals increased statistical power in GLMM relative to GLUM.

Variances

Contrast Variances:

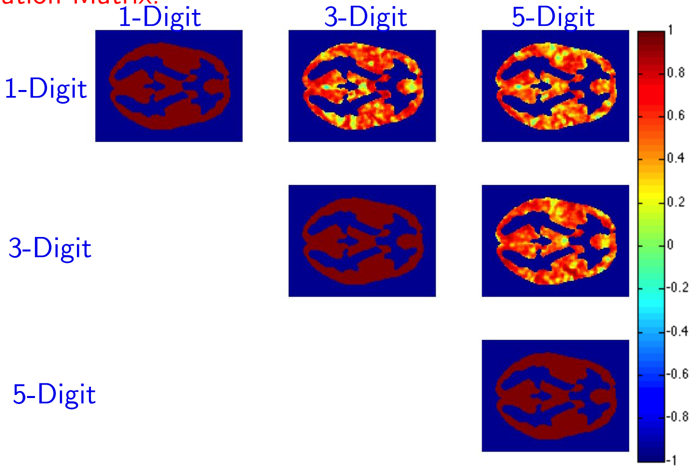
GLMM	GLUM



- The GLUM produces larger variances and will thus sacrifice statistical power.
- $\theta = [\text{task3} - \text{task1}]_{\text{Controls}} - [\text{task3} - \text{task1}]_{\text{Patients}}$

Task Correlations

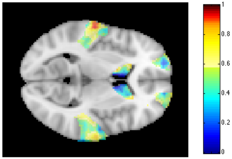
Correlation Matrix:



- The GLMM yields estimates of correlations between the three working memory loads (stage I contrasts).

Summary

- Mass univariate and multivariate linear models produce identical estimates of task-related changes.
- Multivariate modeling approaches consider dependencies between multiple dependent variables
  - Multiple effects/contrasts
  - Multiple voxels [Bowman et al., 2008; Zhang et al., 2012]
  - Multiple time points (e.g. longitudinal study)
- By accounting for correlations, multivariate methods generally
  - Increase efficiency (reduces variability)
  - Increase statistical power.
- Univariate approaches may have a deleterious effect on inference.



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