An Introduction to Statistical Modeling in MATLAB and SPM

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Outline

- What is voxel?
- fMRI Experimental Design
- The General Linear Model
- Contrasts
- Implementation in MATLAB
- Implementation in SPM
- Caveats
- Review
Brain Imaging

- After processing....
Brain Imaging

- The data:
  http://labs.jam3.ca/category/voxel-engine-jam3-labs/
Brain Imaging

- From the beginning (almost)....

A 4 x 6 x 7 voxel 3D image volume.
fMRI Experimental Design
fMRI Experimental Design

- Event-related/Epochs
  - Slow
  - Rapid
- Block
- Mixed Block Event
Neural Activity and BOLD

(Adapted from Bucker 2003)
General Linear Model (GLM)

\[ Y = aX + b \]
Analyses steps in the GLM

(1) Does an analysis of variance separately at each voxel
(2) Makes statistic from the results of this analysis, for each voxel
(3) Inferences
The General Linear Model

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p + \varepsilon \]

- \( Y \quad \rightarrow \quad \text{Vector of Values for each time point / image} \)
- \( \beta_0, \beta_1, \ldots, \beta_p \quad \rightarrow \quad p+1 \text{ fixed but unknown parameters} \)
- \( X_1, X_2, \ldots, X_p \quad \rightarrow \quad p \text{ vectors of } n \text{ predictor values} \)
- \( \varepsilon \quad \rightarrow \quad \text{Vector of } n \text{ error values} \)

Typical Assumptions:
- Proposed model is correct
- \( \varepsilon \sim \text{Norm}(0, \sigma^2V) \) where \( V \) is a correlation Matrix
The General Linear Model

\[ Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p + \varepsilon \]

\[ Y_1 = \beta_0 + \beta_1 x_{1,1} + \beta_2 x_{1,2} + \cdots + \beta_p x_{1,p} + \varepsilon_1 \]
\[ Y_2 = \beta_0 + \beta_1 x_{2,1} + \beta_2 x_{2,2} + \cdots + \beta_p x_{2,p} + \varepsilon_2 \]
\[ Y_3 = \beta_0 + \beta_1 x_{3,1} + \beta_2 x_{3,2} + \cdots + \beta_p x_{3,p} + \varepsilon_3 \]
\[ \vdots \]
\[ Y_n = \beta_0 + \beta_1 x_{n,1} + \beta_2 x_{n,2} + \cdots + \beta_p x_{n,p} + \varepsilon_n \]

\[ Y = \hat{Y} + \varepsilon \]

observed = predicted + random error

In Matrix Form

\[ Y = X\beta + \varepsilon \]
Neural Activity and BOLD

(Adapted from Bucker 2003)
X Vectors – Assumed Model

• Canonical HRF

• Derivative Terms

Canonical HRF
Temporal derivative
Dispersion derivative
GLM and fMRI Models

How does this look with data?

Observed data

Model (green and red) and true signal (blue)

Error + noise – set parameters to minimise this
Hemodynamic Response Estimating the Activity Based on Beta

In Matrix Form \[ Y = X\beta + \epsilon \]
What Model Should I Use?

- Block Designs: Assume a Model
- Event-Related Designs:
  - FIR / No Assumed Model
  - Assume a Model + Derivatives
  - Assume a Model
X Vectors -- FIR

\[ \mathbf{X} = \beta_1 \ast \mathbf{X}_1 + \beta_2 \ast \mathbf{X}_2 + \ldots + \varepsilon \]
X Vectors – Canonical + Derivatives
Comparison of Models
Summary of the GLM

\[ Y = X \beta + \varepsilon \]

**Observed data:**
- SPM uses a mass univariate approach – that is, each voxel is treated as a separate column vector of data.
- \( Y \) is the BOLD signal at various time points at a single voxel.

**Design matrix:**
- Several components which explain the observed data, i.e., the BOLD time series for the voxel.
- Timing info: onset vectors, \( O_{mj} \), and duration vectors, \( D_{mj} \).
- HRF, \( h^m \), describes shape of the expected BOLD response over time.
- Other regressors, e.g., realignment parameters.

**Parameters:**
- Define the contribution of each component of the design matrix to the value of \( Y \).
- Estimated so as to minimise the error, \( \varepsilon \), i.e., least sums of squares.

**Error:**
- Difference between the observed data, \( Y \), and that predicted by the model, \( X\beta \).
- Not assumed to be spherical in fMRI.
MATLAB
MATLAB Basics

- Column Major (rows then columns)
- * versus .* (. Can be used with many functions)
- (),[],{}
- Strings versus numbers
- Variable Names are: a, a1, a3 not a(1) a(2) a{2}
- = versus ==
- 4D data versus 2D processing
- SPM
- Nifti files
Implementation
MATLAB/SPM
Types of Data
Types of Data – Dependent Variable

- Functional Connectivity – Correlation
- Functional Connectivity -- ICA
- Task Data
  - Single Condition
  - Multiple Conditions
  - Multiple Predictors Per Condition
- Context-Dependent Connectivity
- Other Types
Types of Data – Independent Variable

• Group
• Behavioral Data
  • Performance
  • Neuropsychological Scores
  • Emotional Scales
• Age
• Total Brain Volume, Hippocampal Volume, etc.
• Images
Example

- \( Y \) and \( X \)

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<tr>
<th>Scan no</th>
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<th>Task difficulty</th>
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<td>55.82</td>
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<td>11</td>
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</tr>
<tr>
<td>12</td>
<td>55.69</td>
<td>2</td>
</tr>
</tbody>
</table>

\( X \) can contain values quantifying experimental variable
### Parameters & error

\[ Y = \beta x + c + \varepsilon \]

- **\( \beta \):** slope of line relating \( x \) to \( y \)
  - ‘how much of \( x \) is needed to approximate \( y \)?’
- **\( \varepsilon \):** residual error
  - the best estimate of \( \beta \) minimises \( \varepsilon \): deviations from line
  - Assumed to be independently, identically and normally distributed

\( \text{Slope } \beta = 0.23 \)

\( \text{Intercept } c = 54.5 \)
GLM

- Important to model all known variables, even if not experimentally interesting:
  - e.g. head movement, block and subject effects
  - minimise residual error variance for better stats
  - effects-of-interest are the regressors you’re actually interested in
GLM – One Sample T-test
GLM – Paired T-Test
GLM – Two Sample T-Test

• In SPM, the 1s will change if the variance is not equal and is set to unequal
GLM – Multiple Regression
GLM – Repeated Measures
GLM – Biological Parametric Mapping

Technical Note

Biological parametric mapping: A statistical toolbox for multimodality brain imaging

Ramon Casanova, a, R
Satoru Hayasaka, a, c
Ly

Group 1 Group 2 ROI mean

A SPM ANCOVA

Group 1 Group 2

B BPM ANCOVA

Group 1 Group 2 GM-VBM

Jonathan H. Burdette, a
jian a
Implementation
MATLAB/SPM
Statistical Tests
Statistical Tests

- T-Test
- F-Test
Implementing the T-test

\[ c = +1 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ \]

\[ t\text{-test } H_0: c^T \beta = 0 \]

\[ T = \frac{\text{contrast of estimated parameters}}{\sqrt{\text{variance estimate}}} \]

\[ \text{Variance Estimate} \]

\[ \text{Sqrt}(\text{Var} \ast c^T (X^T X)^{-1} c) \]
Fixed Effects Magnitudes, Model-Free Example

- Using the numerator from the T-test, we get $c^*b$ as the magnitude of the effect.

\[
\begin{bmatrix}
-0.46159 & -0.0949 & 0.30717 & 0.4317 & 0.4578 & 0.09565 & -0.30571 & -0.43014
\end{bmatrix} = c
\]

\[
\begin{bmatrix}
-0.13263 \\
-0.11653 \\
0.069775 \\
0.042275 \\
0.119375 \\
0.072575 \\
-0.02633 \\
-0.02853
\end{bmatrix} = b
\]

- $c$ has the unique properties of summing to zero, and in certain cases $c^*c^\top$ is equal to 1. This is the basis for the problem, that will be shown in a few slides.
Fixed Effects Magnitudes, Model-Free Example

- Using the numerator from the T-test, we get $c^*b$ as the magnitude of the effect.

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Graphical Illustration of the contrast matrix

Portions of the contrast matrix and the $\beta$ coefficient matrix.

\[
\begin{bmatrix}
-0.13263 \\
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-0.02633 \\
-0.02853
\end{bmatrix} = b
\]

→ represents a multiplication of two matrix elements

Add the products of the above multiplication to obtain the magnitude.
Fixed Effects Magnitudes, Model-Free Example

- Using the numerator from the T-test, we get \( c^*b \) as the magnitude of the effect.

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\[ \rightarrow \text{represents a multiplication of two matrix elements} \]

Add the products of the above multiplication to obtain the magnitude.
Fixed Effects Magnitudes, Model-Free Example

- Using the numerator from the T-test, we get $c \cdot b$ as the magnitude of the effect.

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Fixed Effects Magnitudes, Model-Free Example

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Portions of the contrast matrix and the \( \beta \) coefficient matrix.

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Add the products of the above multiplication to obtain the magnitude.
Fixed Effects Magnitudes, Model-Free Example

- Using the numerator from the T-test, we get $c^\ast b$ as the magnitude of the effect.

$$\begin{bmatrix}
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Portions of the contrast matrix and the $\beta$ coefficient matrix.

\[\text{represents a multiplication of two matrix elements}\]

\[\text{Add the products of the above multiplication to obtain the magnitude.}\]
Fixed Effects Magnitudes, Model-Free Example

- Using the numerator from the T-test, we get $c^*b$ as the magnitude of the effect.

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Graphical Illustration of the contrast matrix and the $\beta$ coefficient matrix.

\[\text{represents a multiplication of two matrix elements}\]

Add the products of the above multiplication to obtain the magnitude.
Fixed Effects Magnitudes, Model-Free Example

- Using the numerator from the T-test, we get $c \times b$ as the magnitude of the effect.

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Portions of the contrast matrix and the $\beta$ coefficient matrix.

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Fixed Effects Magnitudes, Model-Free Example

- Using the numerator from the T-test, we get \( c^* b \) as the magnitude of the effect.

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Graphical Illustration of the contrast matrix and the \( \beta \) coefficient matrix.

- Represents a multiplication of two matrix elements.
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Fixed Effects Magnitudes, Model-Free Example

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\end{bmatrix} = b
\]

- $c$ has the unique properties of summing to zero, and in certain cases $c^*c^\top$ is equal to 1.
Implementing the F-test

\[ F = \frac{\hat{\beta}^T X^T M \hat{\beta} \cdot (J - p)}{Y^T R Y / p_1} \sim F_{p_1, J-p} \]

\[ H_0: c^T \beta = 0 \]

\[ c = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \]

additional variance accounted for by effects of interest

error variance estimate
Main effect & interactions:
1. Main effect: 1 (subject)
2. Main effect: 2 (group)
3. Main effect: 3 (condition)
4. Interaction: 2 3 (group × condition)

Contrast weights:
1. Main effect of group:
   ones(1,n1)/n1 -ones(1,n2)/n2 MEG zeros(1,nc) ones(1,nc)/nc
   -ones(1n,nc)/nc
2. Main effect of condition
   zeros(1,n1+n2) zeros(1,ng) MEC MEC*[n1/(n1+n2)] MEC*[n2/(n1+n2)]
3. Interaction group x condition:
   zeros(1,n1+n2) zeros(1,ng) zeros(1,nc) MEC -MEC
4. Test for a single regressor in main effect of group (e.g. G1)
   ones(1,n1)/n1 zeros(1,n2) 1 0 ones(1,nc)/nc ones(1,nc)/nc
   zeros(1,nc)
5. Test for a single regressor in main effect of condition (e.g. C2):
   ones(1,n1+n2)/(n1+n2) n1/(n1+n2) n2/(n1+n2) 0 1 0 0 n1/(n1+n2) 0
   0 n2/(n1+n2) 0
6. Test for a single regressor in the interaction group × condition (e.g. G1C2)
   ones(1,n1)/n1 zeros(1,n2) 1 0 0 1 0 0 1 0 0 0 0
7. Test for two single regressor in the interaction group × condition (e.g. G1C1 and G2C1)
   ones(1,n1+n2)/(n1+n2) n1/(n1+n2) n2/(n1+n2) 1 0 0 n1/(n1+n2) 0 0
   n2/(n1+n2) 0 0
Which Test Should I Run?

- **Event-related**
  - Assume a Model $\rightarrow$ T-test
  - Assume a Model + Derivatives $\rightarrow$ Either
  - FIR $\rightarrow$ Either

- **Block Design**
  - T-test
Constructing Contrasts

Main effect & interactions:
1. Main effect: 1 (subject)
2. Main effect: 2 (group)
3. Main effect: 3 (condition)
4. Interaction: 2 3 (group × condition)

Contrast weights:
1. Main effect of group:
Constructing Contrasts

- S1G1C1: [1 zeros(1,10) 1 0 1 0 0 1 0 0 0 0 0]
- S1G1C2: [1 zeros(1,10) 1 0 0 1 0 0 1 0 0 0 0]
- S2G1C1: [0 1 zeros(1,9) 1 0 1 0 0 1 0 0 0 0 0]
- G1: [ones(1,6)/6 zeros(1,5) 1 0 1/3 1/3 1/3 1/3 1/3 1/3 0 0 0]
- G1vsG2: [ones(1,6)/6 ones(1,5)/5 1 -1 0 0 0 1/3 1/3 1/3 -1/3 -1/3 -1/3]
Main effect & interactions:
1. Main effect: 1 (subject)
2. Main effect: 2 (group)
3. Main effect: 3 (condition)
4. Interaction: 2 3 (group × condition)

Contrast weights:
1. Main effect of group:
   \[
   \text{ones}(1,n1)/n1 \quad \text{ones}(1,n2)/n2 \quad \text{MEg} \quad \text{zeros}(1,nc) \quad \text{ones}(1,nc)/nc \\
   -\text{ones}(1n,nc)/nc
   \]
2. Main effect of condition
   \[
   \text{zeros}(1,n1+n2) \quad \text{zeros}(1,ng) \quad \text{MEc} \quad \text{MEc}^*[(n1/(n1+n2))] \quad \text{MEc}^*[(n2/(n1+n2))]
   \]
3. Interaction group x condition:
Implementation
MATLAB/SPM
Inferences
Inferences

• Cluster
  – AlphaSim
  – Extent Threshold
  – SPM8b – False Discovery Rate

• Voxel
  – False Discovery Rate (FDR)
  – Family-wise Error Correction (FWE)
Inferences – AlphaSim/Extent

- Generate X random sets of p-values, smooth them, count the number of voxels in the largest cluster in each set.
- Determine how many voxels are in the largest clusters X% of the time to find the threshold
- Use the result for the extent threshold
Inferences – AlphaSim/Extent

Data set dimensions:
\( nx = 100 \) \( ny = 100 \) \( nz = 25 \) (voxels)
\( dx = 4.00 \) \( dy = 4.00 \) \( dz = 4.00 \) (mm)

Gaussian filter widths:
\( \text{sigmax} = 0.00 \) \( \text{FWHMX} = 0.00 \)
\( \text{sigmay} = 0.00 \) \( \text{FWHMY} = 0.00 \)
\( \text{sigmaz} = 0.00 \) \( \text{FWHMZ} = 0.00 \)

Cluster connection = Nearest Neighbor
Threshold probability: \( p\text{thr} = 5.000000\times10^{-3} \)

Number of Monte Carlo iterations = 1000

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<th>Cl Size</th>
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<th>CumuProp</th>
<th>p/Voxel</th>
<th>Max Freq</th>
<th>Alpha</th>
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<td>1.000000</td>
<td>0.000000016</td>
<td>10</td>
<td>0.010000</td>
</tr>
</tbody>
</table>
Inferences -- FDR

- q% of significant voxels are false positives

- Rank all p-values

- Find max(\(i\)) such that \(p_i \leq i/V^*q\)
  
  - \(V\) is search space
Inferences -- FDR
Caveats
Caveat 1: What is analyzed...

- Missing Data
  - NaN
  - Zeros
Caveat 2: Assumptions

• Cook’s Distance:

\[
D = \frac{e.\hat{2}}{p^* \text{MSE}} \left[ \frac{\text{diag}(X^* \text{pinv}(X)).}{(1 - \text{diag}(X^* \text{pinv}(X))).^2} \right]
\]

if \(\text{max}(D) > \text{finv}(0.5, p+1, n-k-1)\)
\[i = \text{find}(D == \text{max}(D));\]
\[\text{disp}([\text{"Observation ` num2str(i) ` is an outlier. Cook’s Distance was ` num2str(D(i)) `."]]);\]
\[\% \text{ Do something}\]

• Normal Distributions:
Caveat 3: Designs

- Between-subject Designs
- Within-subject Designs
- Mixed Designs
Review
References

- [http://www.fil.ion.ucl.ac.uk/spm/doc/books/hbf2/pdfs/](http://www.fil.ion.ucl.ac.uk/spm/doc/books/hbf2/pdfs/)
- SPM list
- FSL list
- GOOGLE
Acknowledgement

- Aaron Schultz
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- Ron Serlin (UW)
- Reisa Sperling
- Ali Atri