**G8325 - Statistical Methods in functional MRI**

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**Tentative Schedule**

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Note the schedule is tentative and is subject to change as the semester progresses.

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**Some references on MRI/fMRI:**


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**Some more references on MRI/fMRI:**

- Computing Brain Activity Maps from fMRI Time-Series Images, G. Sarty, Cambridge University, 2006

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**Brain Imaging**

- Brain imaging can be separated into two major categories:
  - Structural brain imaging
  - Functional brain imaging

- There exist a number of different modalities for performing each category.

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**Structural Brain Imaging**

- Structural brain imaging deals with the study of brain structure and the diagnosis of disease and injury.

- Modalities include:
  - computed axial tomography (CAT),
  - magnetic resonance imaging (MRI), and
  - positron emission tomography (PET).
Recently there has been explosive interest in using functional brain imaging to study both cognitive and affective processes.

Modalities include:
- positron emission tomography (PET),
- functional magnetic resonance imaging (fMRI),
- electroencephalography (EEG), and
- magnetoencephalography (MEG).

Functional magnetic resonance imaging (fMRI) is a non-invasive technique for studying brain activity.

During the course of an fMRI experiment, a series of brain images are acquired while the subject performs a set of tasks.

Changes in the measured signal between individual images are used to make inferences regarding task-related activations in the brain.

The statistical analysis of fMRI data is challenging.

- It is a massive data problem.
- The signal of interest is relatively weak.
- The data exhibits a complicated temporal and spatial noise structure.
An MR scanner consists of an electromagnet with a very strong magnetic field (1.5 - 7.0 Tesla).

Earth’s magnetic field = 0.00005 Tesla

3 Tesla is 60,000 times stronger than the Earth’s magnetic field.

Magnetic Resonance Imaging

- The subject is placed into the MR scanner.
- The nuclei of $^1$H atoms align with the magnetic field.
- Within a slice of the brain, a radio frequency pulse is used to tip over the aligned nuclei.
- Once the pulse has been removed, the nuclei strive to return to their original aligned positions and thereby induce a current in a receiver coil.
- A signal is created.

Imagine the brain slice to be split into a number of equally sized volume elements (voxels).

We want to construct an image where each voxels’ intensity corresponds to the spatial distribution of the nuclear spin density within the voxel.

The measured signal combines information from the whole brain:

$$S(t) = \int \int \rho(x, y) \, dx \, dy$$

A magnetic field gradient is used to sequentially control the spatial inhomogeneity of the magnetic field, so each measurement can be expressed as:

$$S(k_x, k_y) = \int \int \rho(x, y) e^{-2 \pi i (k_x x + k_y y)} \, dx \, dy$$

By repeatedly altering $(k_x, k_y)$ and making new measurements we can gain enough information to reconstruct $\rho(x, y)$.

The measurements are acquired in the frequency-domain (k-space).
Data Acquisition

$k$-space

IFFT

Image space

Sampling $k$-space

K-space can be sampled in a variety of fashions. Below are two examples:

The resolution of the image depends on the number of points of $k$-space that are sampled.

Spatial Resolution

32x32 image
1024 points sampled in $k$-space

64x64 image
4096 points sampled in $k$-space

128x128 image
16,384 points sampled in $k$-space

MRI studies brain anatomy.

Functional MRI

An fMRI experiment consists of a sequence of individual MR images, where one can study signal changes in the brain.

The data can either be seen as $T$ images of size $N \times N$ or $N^2$ times series of length $T$. 

fMRI studies brain function.

Collect many low-resolution MR images
Temporal series

fMRI

amplitude

voxel time course

One voxel = One timeseries

BOLD fMRI

• The most common approach towards fMRI uses the Blood Oxygenation Level Dependent (BOLD) contrast.

• BOLD fMRI allows us to measure the ratio of oxygenated to deoxygenated hemoglobin in the blood.

• It is important to note that BOLD fMRI doesn’t measure neuronal activity directly, instead it measures the metabolic demands (oxygen consumption) of active neurons.

BOLD Contrast

• Hemoglobin exists in two different states each of which has different magnetic properties and produces different local magnetic fields. (Pauling 1936)
  - Oxyhemoglobin (diamagnetic)
  - Deoxyhemoglobin (paramagnetic)

• Deoxyhemoglobin has the effect of suppressing the MR signal.

• As the concentration of deoxy decreases the signal increases.

HRF

The hemodynamic response function (HRF) represents changes in the fMRI signal triggered by neuronal activity.

Properties of the HRF

• Magnitude of signal changes is quite small
  - 0.5 to 3% at 1.5 T
  - Hard to see in individual images

• The amplitude of the dip is even smaller
  - ~15% of the amplitude of the rise
  - More localized to areas of neural activity

• Response is delayed and quite slow
  - Extracting temporal information is tricky, but possible
  - Even short events have a rather long response

Noise

• In fMRI the noise can be due to both hardware reasons and to the subject.

• Sources of noise:
  - Thermal motion of free electrons in the system.
  - Patient movement during the experiment.
  - Physiological effects, such as the subject’s heartbeat and respiration.
Image Analysis

- The set of measurements (k-space) is made up of the Fourier transform of the image we would like to view.

- Important issues:
  - Data Acquisition
  - Image Reconstruction
  - Resolution
  - Noise
  - Artifacts
  - Reduced k-space sampling

3D Imaging

Sequence of 2D slices

Direct 3D sampling

Experimental Design

- When designing an fMRI experiment one must balance the need for adequate spatial resolution with that of adequate temporal resolution.

Temporal Resolution

- The temporal resolution determines our ability to separate brain events in time.

- In fMRI the temporal resolution is determined by how quickly each individual image is acquired.

- This is given by the repetition time (TR) - one brain image is acquired every TR.

- Typical TR values range from 0.5-4.0 s

Spatial Resolution

- The spatial resolution determines our ability to distinguish changes in an image across different spatial locations.

- Typical image dimensions: 64×64×30 (122,880 volume elements (voxels)). Typical TR: 2 s

Experimental Design

- Block design: Similar events are grouped

  High statistical power to detect activation and robust to uncertainties in the shape of HRF.

  Can’t directly estimate features of the HRF.
Experimental Design

- Event-related design: Events are mixed
  - Allows for the estimation of features of the HRF.
  - Decreased power to detect activation.

Field Strength

- Monkey V1 at 7.0 T vs. Human V1 at 1.5 T

Pre-processing

- Prior to statistical analysis fMRI data undergoes substantial preprocessing.
  - Pre-processing steps include:
    - Slice time correction
    - Motion Correction
    - Normalization
    - Spatial Filtering
    - Temporal Filtering

Slice Time Correction

- In fMRI the brain volume is typically sampled slice-by-slice (i.e. 2D imaging; not 3D).
  - Since the slices are acquired sequentially, they are measured at different time points.
  - We need to correct for this when analyzing the data.

Head Motion

- Head movement during an experiment can be a major source of error if not treated correctly.
  - The location of a voxel is assumed to be static across time.
  - Unless properly dealt with head motion may make this assumption invalid.

Normalization

- The brain size of two subjects can differ by up to 30%. They may also vary in shape.
  - Normalization allows one to stretch, squeeze and warp each brain so that it is the same as some standard brain.
Spatial Smoothing

- It is common to spatially smooth the acquired data prior to performing statistical analysis.
- It typically involves blurring the fMRI images using a Gaussian filter.
- This can help increase the signal-to-noise ratio, as well as validate certain statistical assumptions.

Statistical Analysis

- There are multiple goals in the statistical analysis of fMRI data.
- They include:
  - localizing brain areas activated by the task;
  - determining networks corresponding to brain function; and
  - making predictions about psychological or disease states.

Localizing Activation

- The general linear model (GLM) is the dominant approach towards localizing regions of activity in an fMRI experiment.
- It models the data as a linear combination of various signal components and noise.
- The signal components are assumed to have known shapes, but their amplitudes are unknown and need to be estimated.

Modeling fMRI Data

In the GLM framework the time course from each voxel is modeled as a linear combination of various predictors describing the different aspects of the signal.

\[
\text{Signal} = \text{Signal Components} + \text{Noise}
\]

Illustration

Signal and noise.

\[
\text{Signal} = \text{Signal Components} + \text{Noise} + \text{ERROR} \times \beta_1 + \beta_2
\]

Want to test \( H_0: \beta_2 = 0 \)
Matrix Notation

We can write the GLM as follows:

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

as

\[
\begin{bmatrix}
Y_1 \\
Y_2 \\
\vdots \\
Y_n
\end{bmatrix} = 
\begin{bmatrix}
1 & X_{11} & \cdots & X_{np} \\
1 & X_{12} & \cdots & X_{p2} \\
\vdots & \vdots & \ddots & \vdots \\
1 & X_{1m} & \cdots & X_{pm}
\end{bmatrix}
\begin{bmatrix}
\beta_1 \\
\beta_2 \\
\vdots \\
\beta_p
\end{bmatrix}
+ 
\begin{bmatrix}
\varepsilon_1 \\
\varepsilon_2 \\
\vdots \\
\varepsilon_n
\end{bmatrix}
\]

MRI Data Design matrix Model parameters Noise

Model Building

• The design matrix specifies how the factors of the model change over time. It can include terms corresponding to the:
  - Bold response
  - Drift
  - Head movement
  - Physiological effects

• We also need to model the noise.

BOLD Response

• Predict the shape of the BOLD response to a given stimulus pattern. Assume the shape is known and the amplitude is unknown.

• The relationship between stimuli and the BOLD response is typically modeled using a linear time invariant (LTI) system.

• In an LTI system the impulse (the neuronal activity) is convolved with the impulse response function (the HRF).

Drift

• Often slow changes in voxel intensity over time is present in the signal.

• These changes are not related to neuronal activity and are considered a nuisance parameter.

• Scanner instabilities and not motion or physiological noise may be the main cause of the drift, as drift has been seen in cadavers.

Noise Models

• Studies have shown that fMRI noise exhibits temporal autocorrelation.

• Commonly used noise models include:
  - AR(p)
  - AR(1)+WN
  - ARMA(1,1)
  - 1/f - noise

Convolution Examples

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<td>Predicted Response</td>
<td>Predicted Response</td>
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Convolution

Examples
Hypothesis Testing

• After defining the design matrix we are ready to fit the model to voxel-wise fMRI data.

• Using the estimated model parameters we perform hypothesis tests.

• We are often interested in determining whether there is a significant BOLD response in each voxel or whether there are significant differences between tasks.

Example – Two Tasks

\[ \begin{align*}
\text{We may want to test:} & \quad H_0: \beta_2 = 0 \\
\text{or} & \quad H_0: \beta_2 = \beta_3
\end{align*} \]

Statistical Images

• Separate tests are performed at each voxel. The results are summarized in a statistical image.

• An appropriate threshold needs to be chosen to determine which voxels are active.

Multiple Comparisons

• In brain imaging we often test on the order of 100,000 hypothesis tests at a single time.

• At the 5% level of significance we would actually expect to get 5,000 false positives!

• We need to make appropriate correction for multiple comparisons.

• This includes controlling the:
  - Family Error Rate (e.g., Gaussian Field Theory)
  - False Detection Rate (FDR)

Statistical Parametric Map

• The results of the thresholded statistical images are presented in a statistical parametric map.

• Each voxel is color-coded according to the size of its p-value.

Multi-subject Data

• fMRI experiments are often repeated for several runs in the same session and several subjects drawn from a population.
Multi-level Modeling

- **Multilevel models** have been developed for analyzing hierarchically structured data.
- The full **first level model** can be written:
  \[ Y = X\beta + \epsilon \quad \epsilon \sim N(0, \Sigma) \]
- The **second level model** can be written:
  \[ \beta = X_g\beta_g + \eta \quad \eta \sim N(0, \Psi) \]

Illustration

Mixed-effects Model

- The **two-level model** can be combined into a single level model:
  \[ Y = X\beta + \epsilon \]
  \[ = X(X(X\beta + \eta) + \epsilon) \]
  \[ = XX\beta + XX\eta + \epsilon \]
- Classic formulation of a **mixed-effects model**.
- In this model: \[ Y \sim N(XX\beta, XX\eta + \epsilon) \]

Brain Networks

- Human brain mapping has been primarily used to provide maps that show which regions of the brain are activated by specific tasks.
- Recently, there has been an increased interest in augmenting this type of analysis with **connectivity studies** that describe how various brain regions interact and how these interactions depend on experimental conditions.

Connectivity

**Functional Connectivity**

Undirected association between two or more fMRI time series.

**Effective Connectivity**

Directed influence of one brain region on the physiological activity recorded in other brain regions.

Functional Connectivity

**Functional connectivity** analysis is usually performed using data-driven transformation methods which make no assumptions about the underlying biology.

Methods include:

- **Principal Components**
- **Partial Least Squares**
- **Independent Components Analysis**
Effective Connectivity

Effective connectivity analysis is performed using statistical models which make anatomically motivated assumptions and restricts inference to networks comprising of a number of pre-selected regions of interest.

Methods include:
- Structural Equation Modeling
- Dynamic Causal Modeling
- Granger Causality

Prediction

- There is a growing interest in using fMRI data for classification of mental disorders, brain-based nosology, and predicting the early onset of disease.

- Various multivariate pattern classification approaches have successfully been applied to fMRI data.

- Here a classifier is trained to discriminate between different brain states and then used to predict the states in a new set of data.

Multi-modal Experiments

- There is a trend towards increasingly interdisciplinary approaches that use multiple imaging modalities to overcome some of the limitations of each method used in isolation.

- Examples include:
  - Combined EEG and fMRI
  - Combined DTI and fMRI
  - Combined TMS and fMRI