Medical Image Analysis

Instructor: Moo K. Chung
mchung@stat.wisc.edu

Lecture 14.
fMRI time series analysis

March 27, 2007
Example of fMRI: functional MRI in amygdala in picture showing experiment

- Right Amygdala
- Left Amygdala
- Background Noise
- Stimuli
fMRI analysis framework

- fMRI time-series
- Motion correction
- Smoothing
- Spatial normalisation
- kernel
- Design matrix
- General Linear Model
- Parameter Estimates
- Statistical Parametric Map
- fMRI time-series
- Standard template

Source: Gary Huang
Linear systems

• System = input --> output
  Stimulus or Neural activity
    --> functional MRI responses

• System is linear if shows two properties
  Homogeneity (Scalability) & Superposition
Homogeneity

Superposition

Source: Stephen Engel
Subtracting responses
Modeling linear system

\[ y(t) = \int_0^t H(t - s) f(s) ds + e(t) \]

Observed fMRI signal \( y(t) \)
HRF(hemodynamic response function) \( H(t) \)
Gaussian random process \( e(t) \)
Example: Impulse and HRF relation

black: stimuli
red: response
Drift of magnetic fields

\[ y(t) = \int_0^t H(t - s) f(s) ds + e(t) \]

To account for slow drift of magnetic fields, we can add a linear drift term \( at+b \).
Low frequency noise

- Low frequency noise:
  - Physical (scanner drifts)
  - Physiological (aliased)
    - cardiac (~1 Hz)
    - respiratory (~0.25 Hz)
PCA of time series

Source: Keith Worsley
Modeling HRF

\[ y(t) = \int_0^t H(t - s)f(s)ds + e(t) \]

Various models for HRF:
Lange and Zeger (1997): a gamma function
Friston (1998): difference of two gamma functions
Example: pain perception

Alternating hot and warm stimuli separated by rest (9 seconds each).

Hemodynamic response function: difference of two gamma densities

Responses = stimuli * HRF, sampled every 3 seconds

Source: Keith Worsley
Modeling the delay of the response: Keith Worsley

- Delay or latency to the peak of the HRF is approximated by a linear combination of two optimally chosen basis functions:

\[
HRF(t + \text{shift}) \sim basis_1(t) w_1(\text{shift}) + basis_2(t) w_2(\text{shift})
\]

- Convolve bases with the stimulus, then add to the linear model
HRF modeling using the tent function

- Simplest set of such functions are closely related to stick functions: **tent functions**
  \[ T(x) = \begin{cases} 
  1 - |x| & \text{for } -1 < x < 1 \\
  0 & \text{for } |x| > 1 
\end{cases} \]

- Expansion in a set of spaced-apart tent functions is the same as linear interpolation
  \[ \beta_0 \cdot T\left(\frac{t}{L}\right) + \beta_1 \cdot T\left(\frac{t-L}{L}\right) + \beta_2 \cdot T\left(\frac{t-2L}{L}\right) + \beta_3 \cdot T\left(\frac{t-3L}{L}\right) + \ldots \]

_N.B.: 5 intervals = 6 \beta weights_
Discretizing integral

\[ y(t) = \int_0^t H(t - s)f(s)ds + e(t) \]

\[ y(t) = \sum_{t_j \leq t} H(t - t_j)f(t_j) + e(t) \]

\[ y(j) = H(j)f(0) + H(j - 1)f(1) + H(j - 2)f(2) \cdots + H(j - p)f(p) + \epsilon(j) \]

Assumption: HRF decays to zero after time lag \( p \).
Matrix formulation

\[
y(0) = H(0)f(0)
\]
\[
y(1) = H(1)f(0) + H(0)f(1) + e(1)
\]
\[
y(2) = H(2)f(0) + H(1)f(1) + H(0)f(2) + e(2)
\]
\[
y(3) = H(3)f(0) + H(2)f(1) + H(1)f(2) + H(0)f(3) + e(3)
\]

\[
y = XH + e
\]

\[
X = \begin{pmatrix}
  f(0) & 0 & \cdots & 0 \\
  f(1) & f(0) & \cdots & 0 \\
  f(2) & f(1) & f(0) & 0 \\
  \vdots & \vdots & \vdots & \ddots \\
  f(m) & f(m-1) & \cdots & f(m-p)
\end{pmatrix}
\]

: Toeplitz matrix
MATLAB

```matlab
>> toeplitz(1:10)

ans =

   1     2     3     4     5     6     7     8     9    10
   2     1     2     3     4     5     6     7     8     9
   3     2     1     2     3     4     5     6     7     8
   4     3     2     1     2     3     4     5     6     7
   5     4     3     2     1     2     3     4     5     6
   6     5     4     3     2     1     2     3     4     5
   7     6     5     4     3     2     1     2     3     4
   8     7     6     5     4     3     2     1     2     3
   9     8     7     6     5     4     3     2     1     2
  10     9     8     7     6     5     4     3     2     1
```
**periodic impulse function**

```matlab
>> toeplitz([1 0 0 0 0 1 0 0 0 0 1 0 0 0 0])
```

```plaintext
ans =

```
1 0 0 0 0 1 0 0 0 0 1 0 0 0 0
0 1 0 0 0 0 1 0 0 0 0 1 0 0 0
0 0 1 0 0 0 0 1 0 0 0 0 1 0 0
0 0 0 1 0 0 0 0 1 0 0 0 0 1 0
0 0 0 0 1 0 0 0 0 1 0 0 0 0 1
1 0 0 0 0 1 0 0 0 0 1 0 0 0 0
0 1 0 0 0 0 1 0 0 0 0 1 0 0 0
0 0 1 0 0 0 0 1 0 0 0 0 1 0 0
0 0 0 1 0 0 0 0 1 0 0 0 0 1 0
0 0 0 0 1 0 0 0 0 1 0 0 0 0 1
1 0 0 0 0 1 0 0 0 0 1 0 0 0 0
0 1 0 0 0 0 1 0 0 0 0 1 0 0 0
0 0 1 0 0 0 0 1 0 0 0 0 1 0 0
0 0 0 1 0 0 0 0 1 0 0 0 0 1 0
0 0 0 0 1 0 0 0 0 1 0 0 0 0 1
```
Simple linear model approach

\[ y = XH + e \]

\[ \hat{H} = (X'X)^{-1}y \]

• This estimation gives us the height of HRF at each time point.

• Nonparametric HRF estimation technique: estimates HRF as a linear combination of smooth basis functions.
Event related design: Multiple stimuli

\[ y = X_1H_1 + X_2H_2 + X_3H_3 + e \]
Design Matrix

easy to incorporate different runs and subjects
fMRI experiment of picture showing

Snake attacking

subject 1

left

right

subject 2
Are you seeing any pattern?

Snake crawling

subject 1

subject 2

left

right
Now we are see something

Subject 1

Kernel smoothing

left

right

left

right
subject 2

Kernel smoothing

left

right

left

right
Problem with Ordinary Least Squares (OLS) Estimation

• OLS is inefficient since it does not take care of temporal correlation.

• More false positives (Burock et al., 1998; Dale, 1999, Woolrich et al., 2001; Purdon et al., 2001; Wicker and Ponlupt, 2003)

• To address these problems, we model temporal correlation via the whitening process.
HRF  snake attacking  snake crawling  fish swimming

Black: least squares estimation
Red: generalized least squares estimation
Modeling correlated error

\[ y(t) = \int_0^t H(t - s) f(s) \, ds + e(t) \]

Autoregressive model (AR) models

- **AR(3)**: Bullmore et al., (1996)
AR(p) model

e(t) = c_1e(t - 1) + \cdots + c_pe(x - p) + \epsilon(t)

White noise with zero mean and finite variance

• Time series e(t) is called an autoregressive (AR) process of order p and denoted AR(p)

• This model correlates the time series up to p lags.
AR(1) model

\[ e(t) = \rho e(t - 1) + \epsilon(t) \]

Gaussian white noise \( \epsilon(t) \approx N(0, \sigma^2) \)

\[ E[e(t)] = 0 \quad V[e(t)] = \frac{\sigma^2}{1 - \rho^2} \]

(auto) covariance: \( Cov[e(t), e(t - p)] = \frac{\sigma^2}{1 - \rho^2 \rho^p} \)

(auto) correlation: \( corr[e(t), e(t - p)] = \rho^p \)
Higher order AR model?

AR(1) seems to be adequate

... has little effect on the T statistics:

No correlation
Covariance matrix of noise

\[ y = XH + e \]

- Estimate residual from LSE: \( e = y - X(X'X)^{-1}X'y \)
- Estimate covariance matrix: \( V = (V_{ij}) = E(ee') \)

\[
V_{ij} = \text{Var}[e(1)] \text{corr}[e(i), e(j)]
\]

For AR(1) model, the covariance matrix has a special form:

\[
\frac{\sigma^2}{1 - \rho^2}, \quad \rho^{|i-j|}
\]
Covariance matrix = Toeplitz matrix

\[ V_{ij} = \text{Var}[e(1)]\text{corr}[e(i),e(j)] \]

\[ V = \frac{\sigma^2}{1 - \rho^2} \begin{pmatrix} 1 & \rho & \rho^2 & \cdots \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \cdots & \rho^2 & \rho & 1 \end{pmatrix} \]

Variance

autocorrelation
• Estimating autocorrelation at lag $l$

$$\text{corr}[e(t), e(t - l)] = \frac{E[e(t)e(t - l)]}{E[e^2(t)]}$$

• Sample autocorrelation at lag $l$

$$\frac{\sum_{j=l}^{n} [e(j)e(j - l)]}{\sum_{j=1}^{n} e^2(j)}$$
Generalized Least Squares (GLS) Estimation

\[ y = XH + e \]

- Whitening process:
  \[ V^{-1/2}y = V^{-1/2}XH + V^{-1/2}e \]

  Noise is uncorrelated now

- GLS estimation:
  \[ \hat{H} = (X'V^{-1}X)^{-1}X'V^{-1}y \]
Estimating autocorrelation at the left amygdala
Estimating autocorrelation at the right amygdala
Whitening of noise by GLS

Black: autocorrelation via LSE
Red: autocorrelation after whitening
HRF reconvolved with the initial stimuli

- Black: HR based on LSE
  Red: HR based on GLE

- GLE can get the dip while LSE can not obtain the dip.
What do we do with the HRF estimation?

1. Inference on the height of HRF
2. Inference on the area under HRF

Group comparisons via GLM (t or F tests)

Other issues in fMRI analysis:
Fourier analysis of fMRI
Signal filtering/smoothing
Effect of tissue volume to fMRI analysis
Low frequency noise reduction via Fourier transform

• Low frequency noise:
  – Physical (scanner drifts)
  – Physiological (aliased)
    • cardiac (~1 Hz)
    • respiratory (~0.25 Hz)

Aliasing: misidentification of signal frequency

power spectrum

noise
signal

power spectrum
Diffusion smoothing/filtering

- generalization of Gaussian kernel smoothing
- spatially and temporally adaptive filter
Effect of tissue density on fMRI analysis
Publicly available fMRI data analysis tools

• SPM5
• AFNI+SUMA package (SUMA enables surface-based fMRI analysis)
• FMRISTAT (Keith Worsley’s own MATLAB tools)
Connectivity/correlation analysis in fMRI analysis

scatter plot of left and right amygdala fMRI for two subjects

Basic scientific question: how two fMRI time series are related?
Single seed functional connectivity analysis
From a single seed, we compute correlation for every other voxels

High correlation

Source: Keith Worsley
Correlation analysis showing no connection.

PCA showing connection.

(PCA constructed out of correlation matrix)
Multiseed functional connectivity analysis

Partial correlation, partial multiple correlation and canonical correlation can be used.

Source: Tim Cootes
Lecture 15 Topics

Similarity Measures in Image