fMRI Experimental Design
-- a Linear System Perspective

David C. Zhu, Ph.D.
Cognitive Imaging Research Center
Departments of Psychology and Radiology
Reading materials:

Chapter 9

3D Deconvolution Analysis of fMRI Time Series Data (at least Pages 1 to 10)
Engineering Process

- Cognitive Neuroscience Question
- fMRI Question
- Experimental Design
- Pilot Data
- Full Data Acquisition
- Data Analysis

Looping

Time & $
Mechanisms of BOLD (Blood Oxygen Level-Dependent) fMRI

Stimulation

Neuronal Activity

CMR\textsubscript{glucose}

CMR\textsubscript{O2}

Cerebral Blood Volume (CBV)

Blood Oxygen Level

Cerebral Blood Flow (CBF)

Blood Magnetic Susceptibility Effects

Oxygenated hemoglobin: diamagnetic
Deoxygenated hemoglobin: paramagnetic

1/T\textsubscript{2*}

1/T\textsubscript{1}

fMRI Image Signal Intensity

Springer CS Jr, Patlak CS, Palyka I and Huang W. “Principles of susceptibility contrast-based functional MRI: …
System with operator $T$

$$y(t) = T\{f(t)\}$$

1. Find $T$ => Event-related design

2. Assume $T' = T$ based on some model
   - Find expected $y'(t) = T'\{f(t)\}$
   - Compare $y(t)$ and $y'(t)$
   => Block related design
Linear System

- $f(t) \rightarrow \text{System} \rightarrow y(t)$
- $g(t) \rightarrow \text{System} \rightarrow z(t)$
- $af(t) + bg(t) \rightarrow \text{System} \rightarrow ay(t) + bz(t)$
- $f(t) \rightarrow \text{System} \rightarrow y(t)$
- $f(t-t_0) \rightarrow \text{System} \rightarrow y(t-t_0)$
(A) A single short-duration event

(B) A block of multiple consecutive events
Linear Combination

FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 8.16 (f)
Present for 2 seconds

impulse $\delta(t)$ → System → impulse response $h(t)$

$\delta(t)$

Impulse response

$\text{System}$

Impulse

$h(t)$

Graph of impulse response
Traditional (Slow) Event Related Design

Stimuli

ON 2s 15 s ON 2s 15 s ON 2s 15 s

Response
Block Design

Present 10 pictures
With 2 seconds each
Present for 2 seconds

\[ H \approx \sum_{m=0}^{p} h_m \]

Present 10 pictures
With 2 seconds each

Event related design

Block related design
Rapid Event Related Design

Randomizing the stimuli -> More real life

More stimuli per unit time comparing to traditional event related design -> time efficiency

Design flexibility -> more fun

Modeling of fMRI

\[ y(t) = f(t) \otimes h(t) \ + \ \text{noise} \ (t) \]

\[
= \int_{0}^{t} f(\tau)h(t - \tau) \, d\tau
\]
Continuous: \[ y(t) = f(t) \otimes h(t) = \int_0^t f(\tau)h(t - \tau)d\tau \]

Discrete times: \[ y(n\Delta t) = \sum_{m=0}^{n} f(m\Delta t)h(n\Delta t - m\Delta t)\Delta t \]

In short hand, \[ y_n = \sum_{m=0}^{n} f_m h_{n-m} \]

\[ = \sum_{m=0}^{n} f_{n-m} h_m \]

Assume \( h_m = 0 \) for \( n \geq p \), then

\[ y_n = \sum_{m=0}^{p} f_{n-m} h_m \]

Including constant baseline + linear trend, the MR signal measured

\[ Z_n = y_n + \beta_0 + \beta_1 n + \epsilon_n \]

\[ = \beta_0 + \beta_1 n + h_0 f_n + h_1 f_{n-1} + \cdots + h_p f_{n-p} + \epsilon_n \]

For \( n = p, p+1, \ldots, N-1 \)
Using the matrix notation,

\[
Z = \begin{bmatrix}
Z_p \\
Z_{p+1} \\
\vdots \\
Z_{N-1}
\end{bmatrix},
\]

\[
X = \begin{bmatrix}
1 & p & f_p & \cdots & f_0 \\
1 & p+1 & f_{p+1} & \cdots & f_1 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
1 & N-1 & f_{N-1} & \cdots & f_{N-p-1}
\end{bmatrix}
\]

\[
\beta = \begin{bmatrix}
\beta_0 \\
\beta_1 \\
\vdots \\
h_0 \\
\vdots \\
h_p
\end{bmatrix},
\]

\[
\epsilon = \begin{bmatrix}
\epsilon_p \\
\epsilon_{p+1} \\
\vdots \\
\epsilon_{N-1}
\end{bmatrix}
\]
The MR signal intensity at a voxel from a 7-min run

Baseline signal + linear trend + IRF

Error term

The design matrix (when the stimulus ON and OFF)

\[
\mathbf{Z} = \mathbf{X} \beta + \varepsilon
\]

\[
\hat{\beta} = \begin{bmatrix}
\hat{\beta}_0 \\
\hat{\beta}_1 \\
\hat{h}_0 \\
\vdots \\
\hat{h}_p
\end{bmatrix} = (X^t X)^{-1} X^t \mathbf{Z}
\]
Estimate voxel image signals at first 10 time points with sampling rate of TR = 2.5 sec. Assume hemodynamic response returns to zero after 6 points (15 sec) with the following IRF. Voxel image signal has baseline of 100, and linear trend characterized by a slope of 1.

\[ h_0 = 0, \ h_1 = 1, \ h_2 = 3, \ h_3 = 4, \ h_4 = 3, \ h_5 = -1, \ h_6 = 0 \]

Case 1: \( f_0 = 1 \) (on), the rest of \( f_s \) are off \( (0) \).

Case 2: \( f_0 = 1 \) (on), \( f_1 = \) off, \( f_2 = 1 \) (on), off … \( f_8 = 1 \) (on), off ..
Example 1: 

\[
\begin{align*}
\mathbf{Z} & = \begin{bmatrix} z_0 \\ z_1 \\ z_2 \\ z_3 \\ z_4 \\ z_5 \\ z_6 \\ z_7 \\ z_8 \\ z_9 \end{bmatrix} \\
\mathbf{X} & = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 1 & 2 & 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & 3 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 4 & 0 & 0 & 0 & 0 & 1 & 0 \\ 1 & 5 & 0 & 0 & 0 & 0 & 0 & 1 \\ 1 & 6 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 7 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 8 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 9 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 10 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \\
\beta & = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \\
\epsilon & = \begin{bmatrix} \epsilon_0 \\ \epsilon_1 \\ \epsilon_2 \\ \epsilon_3 \\ \epsilon_4 \\ \epsilon_5 \\ \epsilon_6 \\ \epsilon_7 \end{bmatrix} \\
\end{align*}
\]

\[\mathbf{Z} = \mathbf{X} \beta + \mathbf{\epsilon}\]

\[
\begin{align*}
\mathbf{\hat{Z}} & = \mathbf{X} \hat{\beta} \\
\mathbf{\hat{Z}} & = \begin{bmatrix} \hat{z}_0 \\ \hat{z}_1 \\ \hat{z}_2 \\ \hat{z}_3 \\ \hat{z}_4 \\ \hat{z}_5 \\ \hat{z}_6 \\ \hat{z}_7 \\ \hat{z}_8 \\ \hat{z}_9 \end{bmatrix} \\
\end{align*}
\]

\[
\begin{align*}
1 \times 100 & + 0 \times 1 + 1 \times 0 + 0 \cdots + 0 \\
1 \times 16 & + 1 \times 1 + 0 \times 0 + 1 \times 1 + 0 \cdots + 0 \\
1 \times 16 & + 2 \times 1 + 0 \times 0 + 0 \times 1 + 1 \times 3 + 0 \\
1 \times 100 & + 5 \times 1 + 0 \cdots + 0 + 1 \times (64) + 0 \\
1 \times 16 & + 6 \times 1 + 0 \times 0 + 0 \cdots + 1 \times 0 \\
1 \times 16 & + 7 \times 1 + 0 \cdots + 0 \\
1 \times 100 & + 9 \times 1 + 0 + 0 \cdots + 0 \\
1 \times 100 & + 0 \cdots + 0 \\
\end{align*}
\]
Example #2:

\[ z = X \beta + e \]

\[ Z = \hat{X} \hat{\beta} \]

Estimated

\[ Z \text{ affected by first stimulus only.} \]
\[ Z \text{ affected by both stimuli.} \]
\[ Z \text{ affected by 2nd stimulus only.} \]
\[ Z \text{ affected by 3rd stimulus only.} \]
\[ Z = \beta_0 + kX + \text{Noise} \]
Example

\[
\begin{align*}
\begin{cases}
a_1x_1 + b_1x_2 + c_1x_3 &= 1 \\
a_2x_1 + b_2x_2 + c_2x_3 &= 2 \\
a_3x_1 + b_3x_2 + c_3x_3 &= 3 \\
\end{cases}
\end{align*}
\]

\[
\begin{bmatrix}
a_1x_1 + b_1x_2 + c_1x_3 \\
a_2x_1 + b_2x_2 + c_2x_3 \\
a_3x_1 + b_3x_2 + c_3x_3
\end{bmatrix} =
\begin{bmatrix}
a_1 & b_1 & c_1 \\
a_2 & b_2 & c_2 \\
a_3 & b_3 & c_3
\end{bmatrix}
\begin{bmatrix}
x_1 \\
x_2 \\
x_3
\end{bmatrix}
\]

\[
\begin{bmatrix}
a_1 & b_1 & c_1 \\
a_2 & b_2 & c_2 \\
a_3 & b_3 & c_3
\end{bmatrix}
\begin{bmatrix}
x_1 \\
x_2 \\
x_3
\end{bmatrix} =
\begin{bmatrix}
1 \\
2 \\
3
\end{bmatrix}
\]
\[ Z = X \beta + \varepsilon \]

\[ \hat{\beta} = \begin{bmatrix} \hat{\beta}_0 \\ \hat{\beta}_1 \\ \hat{h}_0 \\ \vdots \\ \hat{h}_p \end{bmatrix} = (X^t X)^{-1} X^t Z \]

Design Evaluation:

(1) Multicollinearity issue

(2) Minimize error

Analogy of Multicollinearity Issue

\[
\begin{align*}
X + Y + Z &= 1 \\
2X + 2Y + 2Z &= 2 \\
3X + 3Y + 3Z &= 3
\end{align*}
\quad \longrightarrow \quad
\begin{align*}
X + Y + Z &= 1 \\
X + Y + 3Z &= 2 \\
X + Y + Z &= 3
\end{align*}
\quad \longrightarrow \quad
\text{Cannot Resolve } X, Y \text{ and } Z
\]

\[
\begin{align*}
X + Y + Z &= 1 \\
X + 3Y + Z &= 2 \\
X + Y + 3Z &= 3
\end{align*}
\quad \longrightarrow \quad
\text{Can resolve } X, Y \text{ and } Z
Repeat

- 6sec-A-6sec-B-6sec-C-6sec ----

2 sec for each stimulus

Prepared by: [Name]

Reviewed by: [Name]

Figure 1: Signal over time (sec)
2 sec for each stimulus

Repeat with Various ISIs

--- 6sec-A-2sec-B-6sec-C-8sec-A-4sec-B-4sec-C---

Better Design

Time (sec)
Repeat with Various ISIs and Random Order of Stimuli

---6sec-A-2sec-B-6sec-C-8sec-B-4sec-B-4sec-A-2sec-A---

2 sec for each stimulus

Signal

Time (sec)
Flanker Study: >>>>>>>> vs. >>>><>>> vs. □□□□ > □□□□

IRF

Time (sec)

Zhu, Zacks and Slade
Null Hypothesis Testing

$H_0$: $\text{sample} = \text{baseline}$ (" + ") in this case

$H_1$: $\text{sample} \neq \text{baseline}$

- **t test**: More active than
  - Less active than
- **F test**: Active
Null Hypothesis Testing

\[ H_0: \gggggggg = \square \square > \square \square \]

\[ H_1: \gggggggg \neq \square \square > \square \square \]

- t test
  - More active than
  - Less active than

- F test
  - Different level of activation
(C) BOLD fMRI signal (arbitrary units)

Time (s)

(D) BOLD fMRI signal (arbitrary units)

Time (s)

- Orange: 1 Stimulus
- Purple: 2 Stimuli
- Black: 4 Stimuli
- Red: 8 Stimuli
- Green: 16 Stimuli
- Blue: 32 Stimuli
Summary

Block Design
Advantage: Best for detection
Easy to implement paradigm
Relative immune to timing error

Traditional (Slow) Event Related Design:
Advantage: No assumption of linear system
Able to characterize IRF

Rapid Event Related Design:
Advantage: More life like
More time efficient
Flexible design
Able to characterize IRF
Hi, I have survived an fMRI study!