Modeling the BOLD response in fMRI

Tutorial MICCAI'04
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Outline

I. Introduction

II. Linear models for brain activity detection

III. Advanced models for dynamical estimation

IV. Future directions
I.1 Origin of fMRI signal: BOLD

BOLD = Blood oxygenation level dependent signal (BOLD)

Intrinsic contrast agent:
- Oxyhemoglobin \([O_2 Hb]\):
  - Diamagnetic
- Deoxyhemoglobin \([HHb]\):
  - Paramagnetic

Neuronal activation

Little increase of \(O_2\) consumption accompanied by a large change of oxygenated blood flow

Ratio of oxygenated blood to deoxy increases with neuronal activity

Results in decreased magnetic susceptibility and increased fMRI signal
I.1 From neuronal activity to the BOLD response

The BOLD signal results from a complex mixture of these parameters.
I.2 The BOLD response (HRF)

- Function of blood oxygenation, flow, volume [Buxton et al. 98]
- Peak (max. oxygenation) 4-6s poststimulus;
- Baseline after 20-30s
- Initial undershoot can be observed [Malonek & Grinvald. 96]
- ... but differences across: other regions [Schacter et al. 97]
- individuals [Aguirre et al. 98]
I.3 Why modeling the BOLD response?

1. Modeling for detection: improved models provide better detection and localization of brain activity
   - For which class of fMRI experiments?

2. Modeling for HRF estimation:
   - Account for variability sources
   - Extract as far as possible information about neuronal activity (hemodynamic delay, repetition-suppression, ...)

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I.3 Blocked vs. Event-related

Source: Buckner 1998
I.3 Block vs. Event-related designs

Simulated time courses using different fixed Inter Trial Intervals [Burock et al. 98]

Block design:
- Higher SNR and small signal variations

ER: Spaced mixed trials
ER: Rapid mixed trials

Normalized % signal change
Time (sec)
I.3 Randomized event-related designs

Simulated time courses using randomized Inter Trial Intervals [Burock et al. 98]

- Rapid trials designs induce **stronger effect**
- **Randomized designs** necessitate accurate HRF models to predict BOLD **signal variations**
I.3 hemodynamic delay estimation

I. Understanding the chronology of activations in single trial fMRI experiments [Kruggel et al. 99]

II. Inferring the causality of underlying neural processes

Delays (sec): \( \text{HG}_L \sim \text{HG}_R < \text{MTG}_R \sim \text{Th}_R \sim \text{Th}_L < \text{FOC}_L \)
II. Basic models for detection: the Generalized Linear Model

1. How to proceed to detect brain activity?

2. The linear regression context

3. More flexible models
II.1 fMRI example

One session

Passive word listening versus rest

7 cycles of rest and listening

Each epoch 6 scans with 7 sec TR

Question: Is there a change in the BOLD response between listening and rest?

Time series of BOLD responses in one voxel

Stimulus function
II.2 Basic linear model

\[ y = \beta_1 X_1 + \beta_2 X_2 + \varepsilon \]

\[ \varepsilon \sim N(0, \sigma^2 I) \]

(error is normal and independently and identically distributed)

Question: Is there a change in the BOLD response between listening and rest?

Hypothesis test: \( \beta_1 = 0 \)?
II.2 Improved model

Convolve stimulus function with model of BOLD response

Hemodynamic response function

fitted data
II.2 Low frequency drift

data and three different models
II.2 noise autocorrelation

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

autoregressive process of order 1 (AR(1))

\[ \varepsilon_t = a \varepsilon_{t-1} + \zeta_t \quad \text{with} \quad \zeta_t \sim N(0, \sigma^2) \]

autocorrelation function
II.2 Inference -- t-statistic

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

boxcar parameter > 0 ?

Null hypothesis: \[ \beta_1 = 0 \]

\[ t = \frac{c^T \hat{\beta}}{\sqrt{\text{Var}(c^T \hat{\beta})}} \]
II.3 Why more flexible models are required in event-related experiments?

1. Signal fluctuations are quicker (piecewise constant model inappropriate)

2. The variability sources are more visible
II.3 Between-subject variability of the HRF [Aguirre et al. 98]

Group 1

Group 2
II.3 Between-scan variability of the 
HRF [Aguirre et al. 98N Duann et al. 02]

Subject 1
less variable

Subject 2
most variable
II.3 Between-region variability of the HRF [Ciuciu et al. 03]

Primary auditory cortex
(-60,-24,4) mm

Planum temporale
(-64,-40,16) mm
II.3 More flexible models

Modeling the variability : How?
II.3 Fourier temporal basis functions

$\{f_k(t)\}_k$ : set of windowed sines & cosines

Any shape (up to frequency limit);
Inference via F-test
II.3 Gamma temporal basis functions

[Lange and Zeger 97], [Cohen 97]

\( \{f_k(t)\}_k \) : bounded, asymmetrical (like BOLD)
Set of different lag and inference via F-test
II.3 Informed basis set [Friston et al. 98]

 Canonical HRF: 2 gamma functions + Multivariate Taylor expansion in:
   — time (Temporal Derivative)
   — width (Dispersion Derivative)

  “Magnitude” inferences via t-test on canonical parameters (providing canonical is a good fit)
  “Latency” inferences via tests on ratio of derivative : canonical parameters
FMRI model in the real life
A language comprehension study [Pallier et al. 02]
II.3 FIR model

Mini “timebins” (selective averaging [Dale 97])

Any shape (up to bin-width)

Inference via F-test

Size of signal

Time after event

5s
II.3 Temporal basis functions: a comparative study

Example: rapid motor response to faces [Henson et al. 01]

Canonical + temporal + dispersion derivatives appear sufficient here... may not be for more complex trials (eg stimulus-delay-response)
III. Advanced models for dynamical estimation

1. Non-parametric estimation of the HRF

2. Nonstationary (trial by trial) estimation of the BOLD response

3. Physiological nonlinear modeling of the neurovascular coupling
III.1 Non-parametric estimation of the HRF

- **Voxelwise methods for ER paradigms:**
  - Linear and time-invariant model (FIR model) [Goutte et al. 00, Marrelec et al. 03]
  - Bayesian analysis with temporal and physiological prior [Woolrich et al. 04]
  - Extension to multi tasks and asynchronous event-related paradigms [Ciuciu et al. 03]; download the HRF toolbox at [http://www.madic.org/download/index.php](http://www.madic.org/download/index.php)

- **Regionwise methods**
  - Compute an average time course in the region-of-interest (ROI) and perform the estimation with a voxel-specific method [Makni et al. 04]
II.3 Modeling the event-related signal [Marrelec et al. 03, Ciuciu et al. 03]

Assumption: Neuronal Event Stream is Identical to the Experimental Event Stream

\[ x_m(t) = \sum_n \delta(t-t_n), \forall m=1,\ldots,M \]

\[ y_j(t_n) = \sum_{m=1}^M \sum_{k=0}^K h_k^m x_m(t_n-k\Delta t) + \sum_{q=1}^Q T_q(t_n)l_q + \varepsilon(t_n), \forall n=1 \ldots N \]

\[ y_j = \sum_{m=1}^M X_m h_j^m + Tl_j + \varepsilon_j \]

fMRI data in \( V_j \)

Gaussian noise

Unknown HRF for the mth event type
III.1 Proposed model for regionwise estimation [Makni et al. 04]

\[ y_j = \sum_{m=1}^{M} a_j^m X^m h + T l_j + \varepsilon_j \quad \text{with } \varepsilon_j \sim N(0, \sigma_j^2 I_N) \]
III.1 Bayesian analysis for regionwise estimation [Makni et al. 04]

I. Gaussian prior information on $\mathbf{h} : \mathcal{N}(0, \tau \mathbf{R})$

II. Prior information on the magnitude coefficients

- Experimental conditions are mutually independent
- HRF response levels for condition $\mathbf{m}$ are $\mathcal{N}(\mu_m, \sigma_m^2)$ - distributed
- No spatial correlation modeled between voxels since such information should be integrated on the cortical surface

III. Bayesian estimation from the posterior distribution

$$p(\mathbf{h}, \mathbf{A}, \mathbf{l}, \theta | Y) = p(Y | \mathbf{h}, \mathbf{A}, \mathbf{l}, \sigma^2) p(\mathbf{h}) p(\mathbf{A} | [\mu_m, \sigma_m^2]_{m=1}^M) p(\mathbf{l}) \prod_m p(\mu_m, \sigma_m^2) \prod_j p(\sigma_j^2)$$
III.1 Estimation results [Makni et al. 04]

Canonical HRF used in SPM

Regionwise HRF estimate

Time in sec

SPM cluster

Voxel-specific response levels

Estimated magnitude coefficients for the condition audio

Statistical t-map contrast: audio-video

ROI: activation cluster defined with SPM (p: 0.001)
III.2 Nonstationary model of the BOLD response [Duann et al. 02]

I. Modeling the trial by trial variability using data-driven methods

- Infomax ICA: determine an unmixing matrix $W$, and spatially independent component activations $M$ such that $M = WY$
III.2 Nonstationary model of the BOLD response [Donnet et al. 04]

- Modeling the trial by trial variability

\[ y(t_n) = \sum_{m=1}^{M} \sum_{j=1}^{J_m} \alpha_{mj} h(t_n - \tau_{mj}) + \sum_{q=1}^{Q} T_q(t_n) l_q + \epsilon(t_n) \]

• Need to estimate the unknown parameters \( \{\alpha_{mj}\}, h, \{l_q\}, \sigma^2 \)

• Smoothness constraint on the HRF: \( h^t R h \leq C_{\text{reg}} \)

[Goutte et al. 00, Marrelec et al. 03]
Estimation issues

I. Parameter estimation problem for $P = \{\alpha_{mj}\}$
   - $M_{P,0}$: model with constant magnitudes: regularized least square criterion
   - $M_{P,1}$: model with trial-varying magnitudes: ML estimation problem using EM-like algorithms [Delyon et al. 02]

II. Model selection problem
   - Choose the best model ($M_{P,0}$ or $M_{P,1}$) for a given family $P$ of size $P$
   - Identify which event types should belong to $P$
   - Select the best family $P^*$ by varying the dimension $P$
Results with nonstationary modeling

Responses to right button click

Responses to visual stimulus

Source: [Donnet et al. 04]

Data from left motor cortex

+/- Standard deviation

HRF estimate $M_{p,1}$

HRF estimate $M_{p,0}$
### III.2 Results about model selection

\[
P = \{ \text{visual}, \text{Right click} \}
\]

Predicted time series by \( M_{P,0} \)

same fMRI data

Predicted time series by \( M_{P,1} \)

Source: [Donnet et al. 04]
III.3 Nonlinear models of the BOLD response

I. Why is it useful to resort to nonlinear models?

- Elucidate the link between physiological variables and the BOLD response
- Infer the neural activation from fMRI data using a blind deconvolution framework (change of time scale)

II. When nonlinear models may be necessary?

- For rapid event-related designs (ITIs < 1 s) to account for saturation or habituation effects
- For EEG-fMRI fusion
III.3 Model linking stimulus to physiological responses [Buxton et al. 04]

The BOLD effect is sensitive to the changes in CBF, CBV and CMR$_{O_2}$
III.3 Balloon model [Buxton et al. 98] [Mandeville et al. 98]

Motivation: CBV returns to baseline more slowly than CBF after the end of the stimulus

Provide a biomechanical mechanism for a delayed CBV return to baseline

Venous compartment = distensible balloon
Balloon model formalism
[Buxton et al. 98, Friston et al. 00]

Blood inflow
\[ \dot{f}_{in} = \epsilon u - \kappa_s f_{in} - \kappa_f(f_{in}) \]

Blood volume
\[ \dot{v} = (f_{in} - f_{out}(v))/\tau \]

Deoxyhemoglobin
\[ \dot{q} = \frac{1}{\tau} (f_{in} \frac{E(f_{in})}{E_0} - f_{out} \frac{q}{v}) \]

Net oxygen extraction fraction:
\[ E(f_{in}) = 1 - (1 - E_0)^{1/f_{in}} \]

BOLD signal
\[ y = \lambda(v, q, E_0) \]

Mean Transit Time through the balloon
\[ f_{out}(v) = v^{1/\alpha} \]

Oxygen extraction at rest

Stiffness coefficient

Viscoelastic effect

Signal decay

Autoregulation

Neural efficacy

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Effects of changing the model parameters on the BOLD response

$\epsilon$: neuronal efficacy

$K_S$: signal decay

$K_f$: autoregulation

$\tau$: transit time

$\alpha$: stiffness

$E_0$: oxygen extraction

$2 \times \epsilon$

$0.5 \times K_S$

$2 \times K_f$

$2 \times \tau$

$2 \times \alpha$

$2.3 \times E_0$

source: [Friston et al. 00]
Parameter estimation issue
[Friston et al. 00], [Riera et al. 04], [Deneux and Faugeras 04]

I. Hidden state space formalism

\[ \dot{X}(t) = F_\theta(X(t), u(t)) + v(t) \]
\[ Y(t) = g_\theta(X(t)) + w(t) \]

Evolution noise
\[ X(t) = \begin{bmatrix} f_{in}(t) \\ \dot{f}_{in}(t) \\ v(t) \\ q(t) \end{bmatrix} \]
[\begin{align*}
\nu(t) & \sim N(0, Q) \\
w(t) & \sim N(0, R)
\end{align*}] 

Observation noise

II. Parameter estimation of \( \theta \) in the ML or MAP sense

Maximize \( \log p(Y|\theta) \) or \( \log p(\theta|Y) = \log p(Y|\theta) + \log p(\theta) \)
Results with nonlinear models

I. Reconstruct the time courses of the state variables

II. Deconvolve the input temporal sequence that best predicts the observed fMRI data

Motor task

Data from motor cortex

State variables time courses

Input sequence
Future directions for intra-subject analysis

I. Combining detection and estimation tasks
   - Multichannel semi-blind deconvolution problem

II. Multimodal fusion of functional neuroimaging data
   - EEG-informed modeling of fMRI time series
   - Integration of anatomical information

III. Real-time analysis of fMRI data
III.3 Nonlinear hemodynamic model
[Friston et al. 00], [Riera et al. 04]

I. Reflect a nonlinear coupling between synaptic activity $u(t)$ and BOLD response built upon the Balloon model $v(t), q(t), E_0$:

Resting blood volume fraction

\[
\lambda(v, q, E_0) = V_0(k_1 (1 - q) + k_2 (1 - \frac{q}{v}) + k_3 (1 - v))
\]

\[
k_1 = 7 E_0, \quad k_2 = 2, \quad k_3 = 2 E_0 - 0.2
\]