Signal Processing for Functional Brain Imaging: Course Introduction

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Signal Processing for Functional Brain Imaging

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leads most lectures

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leads journal club

With lectures contributed by: Dr. Maria Giulia Preti, Dr. Frank Scharnowski, Dr. Silke Anders
Signal Processing for Functional Brain Imaging

- At the interface of
  - Neurosciences, physiology, psychology
  - Engineering, physics, instrumentation
  - Applied mathematics, statistics
The right method for the right question!
- teach general tools: General linear Model, Fourier analysis, principal component analysis, independent component analysis, pattern recognition (machine learning), graph models
- in the context of analyzing brain imaging data (i.e. large noisy data sets!)
LABS and JOURNAL CLUB

- Lab exercises for analysis of actual brain imaging data

- Journal club showing the application of signal processing tools in brain imaging for fundamental and clinical neuroscience. Students will read, present, and critique original research papers. Emphasis on how to structure a scientific presentation.
Course organization

- Instructors
  - Dimitri Van De Ville
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  - Melissa Saenz
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- Room & time: **AAC.137**
  - Main course: 14h-16h
  - Journal club: 16h-17h (6x), 12 groups (Master students)
    - Everybody reads journal article announced week before
    - One student or group presents article using slides,
    - Ph.D. students hand in a small report (1-2 pages) where they discuss one paper in relationship with their Ph.D. research
  - Lab exercises: 15h-17h (2x)
Course organization

- URL of the course
  - http://miplab.epfl.ch/teaching/
  - Slides of the course presentations
  - Additional material and articles
  - background matrix algebra

- Grading
  - Presentation and participation to journal club: 20%
    - Master students: presentation
    - Ph.D. students: presentation or report
  - Written exam: 80%
  - Homework exercises: not graded
Semester overview (update)

- Feb 20: Introduction
- Feb 27: General linear model: basics
- March 6: General linear model: advanced +JC (?)
- March 13: Topographic Mapping + JC (?)
- March 20: General Linear Model Lab + JC (?)
- March 27: Independent component analysis + JC (?)
- April 3: Multimodal imaging + JC (?)
Semester overview (update)

- April 10
  ICA lab + JC (?)

- April 17:
  Pattern recognition

- April 24:
  Easter Holiday

- May 1:
  Real-time fMRI

- May 8:
  Graph Models

- May 15
  Hyperscanning + JC (Guest lecture by Silke Anders)

- May 22: Summary

- May 29: Ascension Holiday
Course introduction

- Why signal processing for functional MRI (fMRI)?
  - What is MRI and fMRI
  - Interpretation by mere visualization is unfeasible
  - Overview of signal processing tools

- Journal club
  - How to structure a successful presentation?

- Neural Basis of the fMRI response
  - neuroscience primer
  - the BOLD response. How does it reflect neural activity?
**functional MRI (fMRI)**

You may have seen ...

Reconstructing visual experiences from brain activity evoked by natural movies

Shinji Nishimoto, An T. Vu, Thomas Naselaris, Yuval Benjamini, Bin Yu, Jack L. Gallant

Supplemental movie S1

Decoding pattern of brain response to previously unseen images

*from Nishimoto* et al., 2011, Current Biology
Unlike EEG (measured at skull), fMRI allows measures from deep inside the brain.

Unlike PET, no radioactive tracers are injected.

Hospitals and many research institutions are equipped with MRI machines.

“High” spatial resolution:
- Typical = 3 mm³
- Very high = 1 mm³ (or less)
Magnetic Resonance Imaging (MRI)

- based on nuclear magnetic resonance (NMR) of hydrogen nuclei

Nuclei in strong magnetic field absorb RF energy. Their magnetization “tips over” and oscillates, emitting detectable NMR signal.
**MRI versus functional MRI (fMRI)**

- **MRI**
  - High resolution (1 mm)
  - Single 3D volume
    - 1x1x1 mm³
    - Takes couple of minutes

- **fMRI**
  - Low resolution (~3 mm)
  - Series of 3D volumes
    - 3x3x3 mm³
    - 20-30 slices
    - Every 2-4 sec
    - During 5-10 minutes
The basic idea behind fMRI: we measure a series of MRI images over time (i.e. a movie) and we test for small fluctuations in signal intensity that are related to neural activity.

- **Series of 3D volumes**
  - 3x3x3 mm
  - every 2-4 sec
  - during 5-10 minutes

Brain activity results in ~1% signal change in the voxel timecourse!
functional MRI (fMRI)

fMRI response to moving vs. static visual stimulation

The result is broad activation of the visual cortex in the occipital lobe.

General Linear Model
from Nishimoto et al., 2011, Current Biology

Machine Learning/Pattern Classification
General Linear Model (GLM)

- Regression: the workhorse of fMRI data processing.
- to find voxels in brain that correlate with a predicted pattern of brain activity (confirmatory analysis)
Fourier Analysis

- representing data as a sum of sinusoidal functions
- application in topographic mapping of sensory surfaces in the brain (e.g. retinotopic, cochleotopic, somatotopic maps)
- applications where we seek the phase of the signal
Principal Components Analysis (PCA)
Independent Components Analysis (ICA)

- “ignorance based” data-driven approach without assumptions about time courses or spatial patterns
- temporal and spatial analysis: moving beyond localization to study networks of brain activity that function together
- dimensionality reduction - using more economical data representations

**review**: matrix algebra primer
Pattern Recognition (machine learning)

Linear discriminant analysis, support vector machine, decision trees, ...

- Classification
  - Supervised learning: training set with known labels
  - Pattern recognition, train generic model

- Clustering
  - Unsupervised learning: separate data in meaningful clusters

See Movie: Researchers at Berkeley decode fMRI brain activity to reconstruct what a subject is seeing.

many applications: image recognition, identification, neural networks, medical diagnosis
Graph Models

Graph models denote the dependence between random variables. In fMRI, to assess functional connectivity between brain areas.

An example of a graphical model. Each arrow indicates a dependency. In this example: D depends on A, ....

**many applications:** computer vision, speech recognition, genetic analysis, modeling of protein structure
“What is essential is invisible to the eye”
Le petit prince, Antoine de Saint-Exupéry, 1943

- Tools for finding signal in the noise.
- Huge datasets: data overload!
- Applying the right tool to the right problem
- Scientific presentation skills (journal club, 20% of grade)
Presentation of original research article
Use slides (Powerpoint, Keynote, etc.)
Organization
  - Title Slide
    - Title, authors, location, journal, year
    - List of methods used (for this course)
  - Background
    - Introduce topic/state of previous knowledge (may search internet images)
    - What is the motivation for the study? (what was the gap in knowledge?)
  - Hypothesis
    - What specifically did the study aim to test?
    - Spoil the ending! Now, before showing any data, tell us what the study claims to find and invite us to evaluate the evidence for that claim(s) in the figures that follow.
Journal Club Presentations

- Organization (con’t)
  - Methods & Results
    - show paper figures. label them (Figure 1, Figure 2c, etc)
    - Usually in order, but not necessarily. If there are too many figures it is your job to digest and select the most important
    - Introduce each figure clearly. e.g. “this figure explains the methods ..” this figure show the key data”, “this figure shows results from a control experiment.
    - Not all paper include a good Methods figure. If needed, make your own diagrams. A simple visual diagram is a lot easier to understand than a lot of words.
    - Walk us through each included data figure: what are the axes?
    - check online for supplementary materials; movies.

- Conclusions and Discussion
  - Summarize the conclusions
  - Critique the study: were the results convincing or not? what were limitations?
  - Interesting next steps?
Part 2: Neural Basis of the BOLD response
Neural Basis of the BOLD response

Does fMRI measure neuronal activity?

NO ...

fMRI creates images of hemodynamic changes that are associated with neuronal activity.
fMRI measures a hemodynamic response called BOLD

1) Neuronal activity increases metabolic demand.

2) To meet metabolic demand, blood supply brings glucose and oxygen to neurons (oxygen in the blood is bound to hemoglobin).

3) Blood flow carrying oxygen leads to a local increase in the concentration of oxygenated vs. deoxygenation hemoglobin.

   • Chance fact: oxygenated hemoglobin is less magnetic than deoxygenated hemoglobin and distorts MR images less (in other words, increases MR signal).

4) So, increase in blood oxygenation leads to local MR signal increase. This is the blood-oxygenation-level dependent (BOLD) response. It is based on intrinsic contrast, nothing is injected.
1) Neurons in a brain region are active (metabolic demand at synapse)
2) Blood flow increases locally bringing glucose and oxygen
   (oxygen is carried by hemoglobin in red blood cells in capillaries)
3) Increase in ratio of oxygenated to deoxygenated hemoglobin
4) Increase in BOLD response
BOLD hemodynamic response function (HRF)

- Series of 3D volumes
  - 3x3x3 mm
  - every 2 sec
  - during 5-10 minutes

Empirically measured HRF from two different brain regions.

Notice the response timing: ~2 sec delay, 4-6 sec to peak, up to 20 sec back to baseline
BOLD hemodynamic response function (HRF)

- Series of 3D volumes
  - 3x3x3 mm
  - every 2 sec
  - during 5-10 minutes

Model of HRF (gamma function) often used in data analysis.

Boynton et al., 1996

Notice the response timing: ~2 sec delay, 4-6 sec to peak, up to 20 sec back to baseline
neuron -
- the basic information processing unit
- 100 billion in the human brain (20 billion in cortex)
- **action potentials** - spikes in membrane electrical potential that transmit information.

synapse -
- Electo-chemical junction between neurons, where one neuron can propagate signal to another.
- 100 trillion in the human brain
- source of most metabolic demand

**Primer: Neurons and neural activity**
Synaptic activity depends on ion gradients across the cell membrane.

**ion channels in neurons** -
- proteins embedded in cellular membrane that allow some ions (sodium $\text{Na}^+$, chloride $\text{Cl}^-$, potassium $\text{K}^+$, and Calcium $\text{Ca}^{2+}$) to diffuse.
- voltage and chemical-dependent gates

**ion pumps** -
- after ion flux regenerate and maintain ion gradients
- consume energy (ATP)
Synaptic activity may be excitatory or inhibitory

neurotransmitters open ion channels:

- **Glutamate is excitatory.** Normally opens channels allowing positive current to flow into neuron (Na$^+$ or Ca$^{2+}$ flow in) - makes the neuron more likely to fire an action potential (~90% of synapses)

- **GABA is inhibitory.** Opens channels allowing positive current to flow out (Cl$^-$ flows in or K$^+$ flows) - makes the neuron less likely to fire an action potential

--- if the sum of excitatory and inhibitory synaptic activity reaches a threshold, the postsynaptic neuron fires an action potential

--- Ion gradients need to be restored after excitatory and inhibitory synaptic currents, so both generate positive metabolic demand! (but excitatory activity dominates)
Adenosine triphosphate (ATP) is the principal energy molecule for cells. ATP is locally generated by breakdown of glucose (glycolysis), a process requiring oxygen.

The brain consumes 20% of blood oxygen, despite being only 2-3% of body weight.

Vascular system must provide supply of glucose and oxygen.
Brain Vasculature

Resolution of BOLD response is ultimately limited by resolution of blood supply

Capillaries in brain 5-10 µm diameter! neuron less then 50 µm from the nearest capillary (bar = 100 µm)

Harrison et al Cerebral Cortex 2002

side note: intra-cerebral capillaries block diffusion on many substances - blood brain barrier.
neural activity --> increased blood flow --> increased blood oxygenation --> increased BOLD

Box 6.1 Width of Ateriole in living mouse brain following electrical stimulation measured with two-photon microscopy. Maximum diameter reached after 3-6 sec.

Astrocytes mediate changes in vessel diameter.
Early ideas that changes in the vascular supply of the brain reflect brain function

Angelo Mosso and Sir Sherrington (end of 19th century)
“…the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity.” (e.g., emotional and intellectual activity)

blood flow to the brain would tip the scale
(not entirely accurate!)
Early fMRI images from Kwong et al. (1992). Visual stimulation was turned ON and OFF. Right panel shows timecourse of region-of-interest in visual cortex.
fMRI response to moving vs. static visual stimulation

The result is broad activation of the visual cortex in the occipital lobe.
BOLD response reflects local neural synaptic activity

Logothetis, et al., 2001 recorded simultaneously in monkey: LFP (sum of all synaptic activity), MUA & SUA (spikes), and BOLD response.

"The BOLD contrast mechanism directly reflects the neural responses elicited by a stimulus."

BOLD response best explained by changes in LFP

Suggests BOLD reflects incoming input and local processing more than spiking activity.
BOLD can be triggered by activity of local excitatory neurons,

specific activation of local excitatory neurons as opposed to mixed interneurons, glia, or passing axonal fibers

optogenetic activation allows establishment of causal relationship

also observed BOLD at downstream target

to express channelrhodopsin (light gated ion channels) specifically targeted to principal excitatory neurons
What you really need to remember from this ...

How is fMRI signal related to neural activity?
neural activity --> increased blood flow carrying oxygen --> increased fMRI response

What is the fMRI response called?
BOLD - Blood oxygenation level dependent

What is the time course of the BOLD response?

What neural activity is reflected in the BOLD response?
BOLD reflects the sum of all excitatory and inhibitory synaptic activity
Looking ahead to next week ...
We want to estimate a statistical parameter representing how well the voxel time course fits the model relative to noise. (using General Linear Model (GLM))

This could be, e.g., a t-statistic. And we need to determine a reasonable statistical threshold (i.e., p-value < 0.05)

Note that the model can be more a lot complex that the one here, and that we have many voxels (~100,000) to deal with!

In the end, we get a visualization of statistical scores that exceed a certain threshold.