Physics Tutorial 5: Functional MRI

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The purpose of this tutorial is to cover material related to functional MRI (FMRI), focusing on some of the basic underlying blood oxygenation level dependent (BOLD) physiology, simulating FMRI data acquisition and simple data analysis. Questions without any asterisks are those that should be attempted by everyone, whereas more challenging questions are marked with one (*) or two (**) asterisks, and should be considered optional. Take these opportunities to think about these questions, and then discuss your answers with your tutor.

At the end of the tutorial period, you will receive a "take-home tutor", which is an annotated version of this tutorial guide that will help you complete the tutorial at home if you don't manage to make it all the way through with your tutor, or if you missed the tutorial session.

Attendance will be taken by the tutors, and marks will be given by participation. If you would like additional feedback or clarification on the tutorial material, you are welcome to submit your questions or comments to Weblearn, and a tutor will provide written feedback for you. Those unable to attend the tutorial must submit answers to all unstarred questions to receive credit for the tutorial.

Part 0 – Getting Started

Download and unzip the file containing the tutorial resources from Weblearn, or if you have access to the FMRIB internal network, copy them into your current directory from here:

~mchiew/GradCourse/5_FMRI

Start MATLAB, and make sure you're inside the tutorial directory (i.e., the folder containing all the tutorial files).

Note to jalapeno00 users: please start with the -nojvm option, "matlab -nojvm"; *this should reduce server CPU load if lots of people are trying to use jalapeno00 simultaneously*

Part 1 – Introduction to BOLD Physiology *[20 – 25 minutes]*

Haemoglobin (Hb) is the component of blood that carries oxygen from the respiratory organs to the rest of the body, including the brain. In its fully oxygenated state Hb is diamagnetic whereas deoxygenated Hb (dHb) is paramagnetic. The presence of dHb increases the magnetic susceptibility difference between vessels and extravascular tissue causing magnetic field gradients.

Question 1.1
Why might the dHb concentration in a vessel change?
dHb concentration in a vessel may change due to a change in local oxygen demand of neurons. Neurons that become more active demand more oxygen which is extracted from the blood. This in turn produces more dHb, given a constant flow and volume of blood. The dHb concentration can also change as a result in altered local blood flow. If the blood flow increases, but the demand for oxygen remains

constant, then the concentration of dHb decreases (less oxygen is extracted per unit blood volume that passes through).

Question 1.2
What effect does a reduction in dHb concentration in a vessel have on the T_2* of surrounding tissue?
If dHb concentration in a vessel decreases the surrounding tissue experiences an increase in T_2 as the magnetic susceptibility difference between vessels and tissue decreases.*

When neurons become more active, the local energy demand increases and more oxygen is extracted from the blood. As brain cells use oxygen to produce energy (in the form of ATP) and brain cells do not have a store of energy (or oxygen), the supply of available oxygen in the blood to this region must increase to meet the increased energy demand.

This haemodynamic response to a localised increase in neuronal activity results in a change in local dHb concentration (i.e. oxygen levels). This in turn leads to a measurable change of the MR signal, referred to as the BOLD (blood oxygenation level dependent) response.

Question 1.3*
From what vessels would you expect the BOLD signal to be most prominent: [arteries & arterioles], [capillaries] or [veins & venules]?
In gradient-echo FMRI, signal from large draining veins primarily contributes to the BOLD response, due to the large "static" field inhomogeneity effects the vessels have on the surrounding tissue. This is due to both the fact that larger vessels have a more widespread field disturbance (leading to greater T2 effects), and that the venous vasculature have the greatest change in oxygenation, leading to a greater magnitude disturbance.*
However, when looking at T2-weighted spin-echo FMRI, the signal contributions from the large draining veins is largely negated by the refocusing action of the spin-echo (because it is large enough to be considered a "static" effect), and BOLD signal contributions arise primarily from the capillary bed and smaller vessels. (See Weisskoff MRM 1994 for a more detailed discussion on this topic)

Question 1.4
Would you expect dHb to increase or decrease with neuronal activation? In practice what happens to T_2* and why?
A much greater increase in cerebral blood flow than is required to compensate for increased oxygen consumption accompanies neural activity. dHb is therefore washed out (lower concentration of dHb in vessel), the effect of magnetic field inhomogeneity surrounding the vessel on nearby tissue is lessened and this manifests as an increase in local MR signal / T_2.*

Extra Information
In a BOLD FMRI experiment we are correlating changes in a signal time-courses caused by fluctuations in local dHb concentration that can be related to neuronal activation. These changes however, are measured from an unknown baseline.

Interpretation of BOLD signal changes can become difficult and uncertain as we cannot quantify the baseline state of the brain. For example in a standard BOLD experiment we have no way of accounting for changes in baseline signal which may occur between, or even within a scan session. This may become problematic when the baseline state of the brain is altered due to drug (e.g. caffeine) or disease influences or when comparing groups which may have systematic differences in baseline state (comparing a disease cohort with healthy controls). These are all important factors when considering the design of a BOLD FMRI experiments.

The interpretability of BOLD signal changes could be improved by making direct quantitative measures of the underlying haemodynamic effects that contribute towards the BOLD signal, i.e. CBF and oxygen extraction fraction (OEF). These measurements would need to be combined with a mathematical model of BOLD signal responses and their relationship with CBF, OEF and other neurovascular measures to extract quantitative information.

Part 2 – FMRI Simulator *[10 minutes]*

Warnings: Please note that we have made a number of simplifications to create this simulator and allow it to run in a reasonably short time. It will show you approximately the right trends when varying parameters but it will not accurately predict the z-stats you will achieve for a given protocol. In particular many of the processing steps performed in FEAT have been neglected here (e.g. pre-whitening, smoothing, clustering etc.). For convenience, any z-stat greater than 9 is set to 9.

In this part of the tutorial we explore how various scanner parameters are likely to affect the functional activation that can be observed using BOLD-based functional MRI.

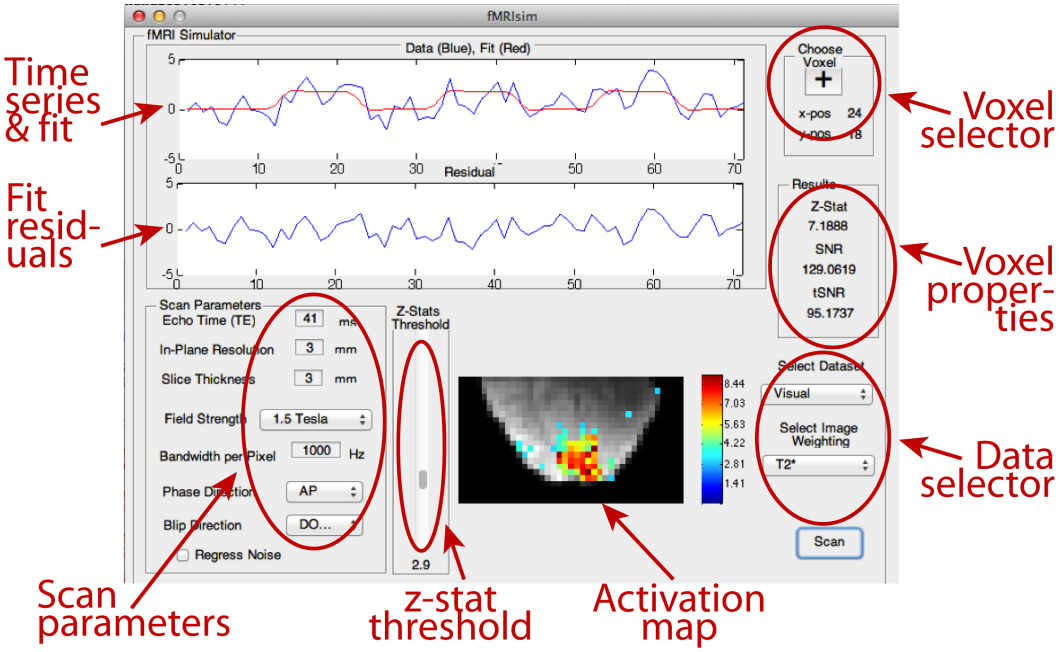

Figure 1

The user interface (see Fig. 1) allows scan parameters to be modified to study the resulting effect on the activation, which is shown overlaid either on a high-resolution structural image (T1) or the simulated EPI data (T2). Once the parameters have been set, press the "Scan" button to run the simulator. You can explore the acquired data by clicking on the "+" symbol on the top right then clicking on a voxel in the image to see the "acquired" voxel time series, the GLM model fit and the residuals (i.e. data – fit) in units of % signal change. In addition, the signal-to- noise ratio (SNR), temporal SNR (tSNR) and z-statistic for this voxel are also shown.*
Demonstrate the simulator to the students, discuss the components, and show the coarse effects of varying resolution, TE etc. on the resulting image/z-stat map.

Discuss the variations in the signal with time in an active voxel.
Launch the simulator via:
```
>> fMRISim
```

Press 'Scan' once to initialise the simulator. The initialization will take a few seconds, but subsequent "scans" should run more quickly.

2.1 Visual Cortex Activation [40-45 minutes]

Ensure the "Visual" data set is selected from the drop-down menu. Set some reasonable parameters for fMRI in GUI:

- *TE = 30 ms*
- *In-plane resolution = 2.5 mm*
- *Slice thickness = 2.5 mm*
- *Field strength = 3T*
- *Bandwidth per pixel = 2500 Hz/px*

Note that the minimum TE you can enter is determined by the bandwidth, so you may need to change the bandwidth first.

Using the "+" button, explore the time-series in voxels with both high and low z-stats (note you will need to click the "+" button each time before selecting a new voxel). Even in voxels with high z-stats the correlation between the data and the paradigm can be surprisingly subtle, but is nevertheless statistically detectable.

Consider the simulated FMRI dataset, with a 10 s off / 10 s on visual stimulus.

The choice of TE in an FMRI experiment is important for determining how sensitive the acquisition is to BOLD signal fluctuations. Recall that gradient-echo BOLD contrast is maximised when TE ~ T2*. Also, it is sometimes useful to think of z-stats like a contrast-to-noise ratio (CNR) measure, where higher z-stats mean greater signal contrast relative to noise levels. In the simulator, it is evident that the z-statistics change when the TE parameter is changed, and that they peak in the range of 30 – 50 ms.
Using the simulator, demonstrate the effect of modifying TE in steps of ~10ms from 20 – 70 ms, and discuss the effect on the z-stats. Consider mentioning that TE not only affects contrast, but artefacts such as signal dropout, but that those effects will be explored in the frontal activation simulations. Here, effects are isolated to contrast changes.

Question 2.1.1
Using a TE = 30 ms, examine the effect on the z-stats when slice thickness is varied from 2 – 12 mm. What happens to the z-stats initially? At what point does this behaviour change? Why might this be?
Initially, as the slice thickness is increased, the z-stats also increase because the voxel volume is larger which increases the SNR and tSNR and therefore the z-stats. This changes at about 6mm. The main reason for this is the partial volume effect. In this simulation we have assumed that the thickness of tissue that is activated with this paradigm is 5mm. Therefore increasing the slice thickness beyond this does not improve the contrast between active tissue and baseline, but does add more signal to the voxel and therefore increases the physiological noise, leading to a decline in z-stats at higher slice thicknesses.
In practice using a higher slice thickness can also lead to increased dropout since thicker slices are more likely to contain a range of precession frequencies, leading to greater dephasing and therefore signal loss. However, those effects are not modelled in this visual experiment simulation.

In addition to TE and slice thickness, choices of in-plane resolution, bandwidth per pixel, and field strength also affect the output z-statistics (and often not independently!).

Exercise 2.1.2
As a group, try to find an optimal protocol (set of parameters) for this simulated visual FMRI experiment. With your tutor, discuss how each change makes the z-statistic image better or worse.
There may be numerous protocols that provide near "optimal" z-stats. One protocol is: Field Strength = 7T, TE = 41 ms, BW/px = 1000 Hz, 2 mm isotropic resolution. Discuss the effects of each parameter on signal contrast and noise. Note that more detailed discussion of physiological noise is contained in the following section. Also, do note that many of these choices also affect artefacts, but that these effects will be simulated in the final section.
Some notes on the parameters:

- *Field Strength: BOLD contrast and SNR increase with field strength, but so does physiological noise. Optimal TE decreases at higher field strengths because T2* decreases.*
- *TE: TE ~ T2* provides optimal contrast, but can impact sequence timing, dropout effects, and may be limited by BW.*
- *Bandwidth: Higher bandwidths increase noise, but allow faster imaging (reduced TE/TR) and reduced distortion.*
- *Resolution: BOLD contrast is maximized when voxel sizes match activation extent. Larger voxels increase physiological noise, but provide better intrinsic SNR. Smaller voxels increase resolution but cost increased scan time. Extended echo-trains lead to dropout/distortion, but at the same time, smaller voxels can have reduced intra-voxel dephasing effects.*

2.2 Noise in FMRI [20 – 25 minutes]

Noise in FMRI is distinct from noise in structural MRI, because a time-series of images are taken, meaning that noise *between* images is just as important as the noise *within* images. Temporal SNR (tSNR) is a term developed to express the SNR with respect to the *between* images noise, whereas SNR refers to the familiar *within* image noise. As you recall, SNR is affected by many different sequence parameter choices. Similarly, tSNR is affected by parameter choices, but also depends on SNR.

Set the field strength to 7T, in-plane resolution to 2mm and slice thickness to 8mm. Select a voxel and vary the bandwidth from 750 Hz/pixel up to 2500 Hz/pixel in steps of 250 Hz/pixel, keeping the echo time constant. At each bandwidth record the SNR and tSNR (temporal SNR) and plot them:

```
>> SNR = [SNR1, SNR2, …, SNR8];
>> tSNR = [tSNR1, tSNR2, …, tSNR8];
>> plotSNR
```

Question 2.2.1
Why does tSNR not equal SNR at each point?
The tSNR is lower than the SNR because of physiological noise which begins to dominate at high SNR values.
Physiological noise increases the signal variation in time (reducing the tSNR) but not across space (so the SNR is the same), leading to the discrepancy between the two measures. This effect is larger at high SNR values since here the thermal noise is relatively small, but the physiological noise is proportional to the signal intensity. In other words, increasing the signal strength relative to the thermal noise above a certain point does not improve the tSNR because the physiological noise is also increased by the same amount.

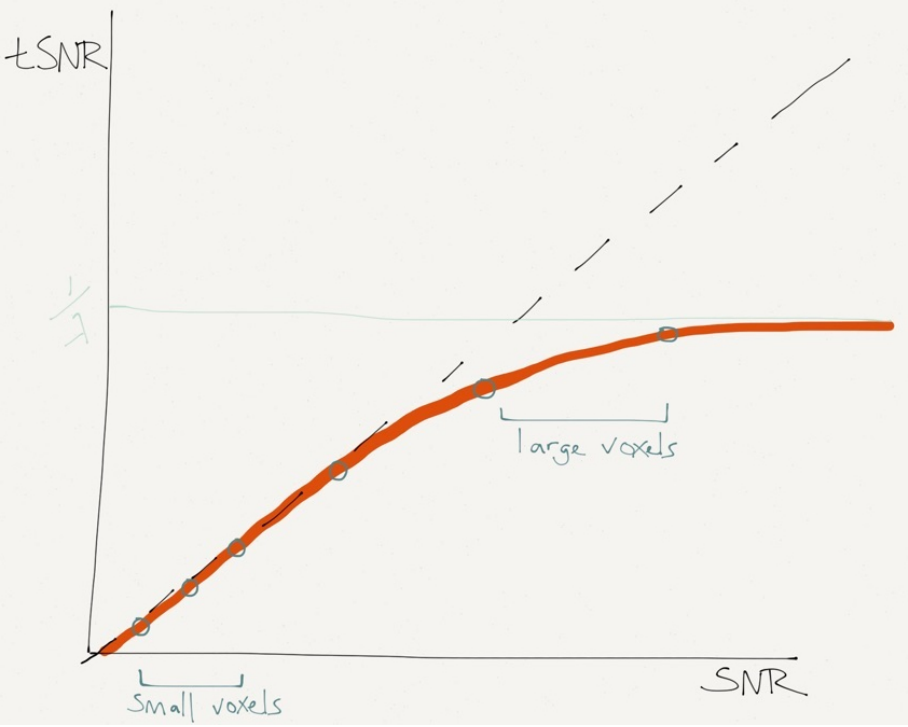

Figure 2

Question 2.2.2**
Given the shape of the tSNR vs. SNR curve in Fig. 2, assuming that $SNR = S/\sigma_0$, that the physiological noise $\sigma_P = \lambda S$, and that $\lim_{SNR\to\infty} tSNR = 1/\lambda$, try to express tSNR as a function of SNR and λ. (Hint, noise terms add in quadrature)

First, define tSNR as the ratio of S with the total noise:

$$tSNR = \frac{S}{\sqrt{{\sigma_0}^2 + {\sigma_P}^2}}$$

Then substitute the definition of σ_P, and re-arrange in terms of SNR:

$$tSNR = \frac{S}{\sqrt{{\sigma_0}^2 + \lambda^2 S^2}}$$

$$tSNR = \frac{\frac{S}{\sigma_0}}{\sqrt{1 + \lambda^2 \frac{S^2}{{\sigma_0}^2}}}$$

$$tSNR = \frac{SNR}{\sqrt{1 + \lambda^2 SNR^2}}$$

For more information, see Kruger & Glover, MRM 2001

Physiological noise is primarily caused by physical fluctuations like breathing and cardiac pulsation. Breathing can induce changes in the local magnetic field homogeneity (by changing the size of the chest cavity), and gross motion of the head with the respiratory cycle is often observed. Cardiac pulsations can lead to variations in signals near blood vessels and fluid cavities (ventricles) due movement and tissue displacement.

When cardiac and respiratory cycles are measured using physiological monitoring equipment (e.g. resipiratory bellows or pulse oximeter), these signals can be used to remove signal components that fluctuate in a similar manner before running FMRI statistical analysis (i.e., the "RETROICOR" method, see Glover et al., *MRM* 2000).
Demonstrate the effect of physiological noise regression on the data time-series and z-statistics (using the Regress Noise checkbox).

Question 2.2.3
When regressing out the physiological noise, why does the tSNR not have exactly the same value as the SNR?
Measuring physiological fluctuations and using these as regressors is certainly likely to remove some of the signal variation due to physiological noise, but this will never be perfect and some residual fluctuations will remain.

2.3 Frontal & Visual Cortex Activation [30 minutes]

Different regions of the brain may need different considerations when planning an FMRI experiment. The brain and head anatomy in visual areas of the brain (occipital lobe) are very different to the structural properties in frontal brain regions.
Discuss with the students what they think might be different about performing fMRI in frontal brain regions compared to the occipital lobe (field inhomogeneity leading to dropout and distortion).

In addition to BOLD contrast and noise considerations, care must be taken in FMRI acquisitions to minimise the impact of magnetic field inhomogeneity on image dropout (*within-voxel* field variation) and distortion (*between-voxel* field variation). As a general rule, decreasing TE reduces signal dropout, and increasing bandwidth reduces image distortion. However, do not forget that these parameters also affect BOLD contrast and noise.
Return to the optimal protocol for observing visual activation at 2mm resolution. Switch to the "Visual + Frontal" using the drop down menu. This is a data set where both visual and frontal areas are activated simultaneously. Try viewing the activation maps on both the simulated EPI data (T2) and the structural data (T1). Note the wrap-around of the back of the brain onto the top of the image (or vice versa) due to image distortion.*

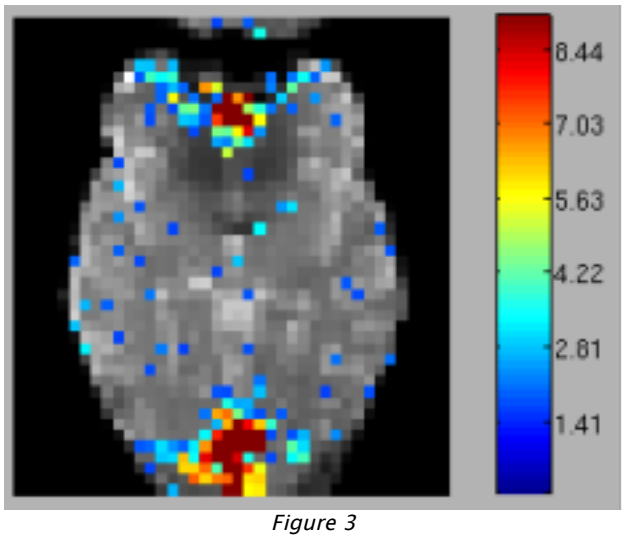

Figure 3

Question 2.3.1
Keeping the protocol the same, we can still see the strong activation at the back of the brain, but why can't we see the frontal activation as clearly? Hint: Depending on your protocol, you may not see any frontal activation at first, but with some parameter tweaking, you should be able to get activation like that shown in Fig. 3. It will probably help to display the activation on top of the T2* image, rather than the T1.
Signal dropout and distortion are more significant in the frontal lobe near the sinuses. Because z-stat "activation" relies on detectable BOLD signal modulation, either dropout and distortion have destroyed the presence of signal, or these regions contain much higher noise levels. In the brain-stem, for instance, FMRI can be difficult because of the presence large magnetic field inhomogeneity, but also additionally because physiological noise is more prominent lower in the brain.

Image artefacts due to magnetic field inhomogeneity are affected by the way the image is encoded in k-space. For example, switching the phase-encoding direction will alter the direction of the artefact, and similarly for "blip-up" vs. "blip-down" encoding.
Demonstrate the effect of various combinations of PE-direction, and blip direction on the output images. Discuss the impact of these choices and how they affect dropout and distortion. Note that PE-direction changes the direction of distortion (ant./post. or left/right), and blip-direction changes whether field-inhomogeneities stretch or squish image features. Neither of these parameters affects the magnitude of dropout (which is only affected by TE), but the location of dropout gets distorted alongside everything else.

Exercise 2.3.2
As a group, try to find an optimal protocol (set of parameters) for this simulated frontal & visual FMRI experiment. With your tutor, discuss how each change makes the z-statistic image better or worse, this time taking into account artefacts.
There may be numerous protocols that provide near "optimal" z-stats. One protocol is: Field Strength = 3T, TE = 24 ms, BW/px = 2000 Hz, 3 mm isotropic resolution PE direction = AP, blip direction = up.

Question 2.3.3*
Given the problems you have seen with EPI, why don't we use other types of pulse sequences to do fMRI?
EPI is incredibly well suited to fMRI since the whole brain temporal resolution is very high whilst still allowing a TE that is suitable to detect BOLD signal changes. Other sequences that produce lower distortion/dropout tend to have reduced sensitivity to the BOLD signal (e.g. spin-echo sequences) or have a much poorer temporal resolution (e.g. 2D-FT GRE).
With more advanced students you may wish to discuss the possibilities of SSFP fMRI, radial trajectories etc.