HST.583

LAB 3: Improving fMRI signal detection using

physiological data

October 17, 2001

Introduction

This Lab examines two ways that physiological data can be used to improve fMRI signal detection.

<u>Cardiac Gating</u>

Part I of this Lab focuses on cardiac gating. This technique uses a subject's EKG recorded during an experiment to improve fMRI signal detection. Cardiac gating is used to overcome a technical difficulty associated with functionally imaging brainstem structures. This difficulty arises because there is considerable cardiac-related, pulsatile brainstem motion. Cardiac gating avoids this problem by (1) synchronizing image acquisitions to the subject heart beat, then (2) correcting image signal strength to account for the variability in interimage interval (TR) that results from fluctuations in heart rate (Guimaraes et. al., 1998).

In this Lab, the effects of cardiac gating are examined for structures in the auditory system. Sounds are processed extensively within auditory brainstem structures, and cardiac gating is important for investigating this processing. The Lab will focus on two particular auditory structures. One is the inferior colliculus. This brainstem structure is a major site of converging projections from both lower and higher brain centers. The second structure is Heschl's gyrus, the site of primary auditory cortex.

<u>Clustered Volume Acquisition (CVA)</u>

Part II of this Lab examines a technique for minimizing the effects of scanner acoustic noise on auditory activation. This technique is called clustered volume acquisition (CVA). Unlike cardiac gating, CVA does not use physiological data recorded during each experiment to improve signal detection. However, the technique is based directly on physiological data, specifically general information concerning the temporal characteristics of fMRI responses (i.e., response latency, duration).

There are two main types of acoustic noise in the imaging environment. One is an on-going noise produced by the pumping of coolant to the magnet. The second, more intense noise is intermittent. It is produced by the scanner gradient coils each time an image is acquired. The noise can pose difficulties for studies using sound stimuli by (1) masking the stimuli, and (2) inducing brain activity that is not related to the stimuli (this noise-related brain activity acts to suppress the fMRI signal changes produced by the intended sound stimuli).

CVA provides a way to reduce the effects of the most problematic noise, namely the noise produced by the gradient coils. CVA involves imaging a volume of slices in a "cluster" and leaving a quiet interval between clusters (Edmister et. al., 1999; Hall et. al., 1999). With this paradigm, the masking effects of the gradient noise can be avoided by

presenting sound stimuli during the quiet interval. In addition, the suppressive effect of the gradient noise on auditory activation can be avoided by (1) making the duration of the image cluster shorter than the onset time of the fMRI response to the first image in the cluster, and (2) making the time between clusters (TR) longer than the fMRI response to a cluster.

The benefits of CVA for detecting activation in auditory cortex were illustrated in lecture. In this Lab, you will examine how these benefits can be extended to subcortical structures by combining CVA with cardiac gating. When CVA is used with a long TR (e.g., $\geq$ 8 sec), image signals are sampled far less frequently than in most fMRI studies. The implications of this lower temporal resolution for experimental design will also be examined in this Lab.

Lab Overview

The organization of the data for this lab is as follows:

Part I: Cardiac Gating (data are in the directory **Lab3.1**)

Part II: Clustered Volume Acquisition (CVA)
>   (a) Combining CVA and cardiac gating (data are in the directory **Lab3.2a**)
>   (b) CVA and temporal sampling (data are in the directory **Lab3.2b**).

The software tools for this lab are programs that run from the command line in the Athena environment:

standard_deviation - generates maps of the standard deviation in image signal over time for every voxel

gating_correction – corrects cardiac-gated data for variations in image signal due to fluctuations in heart rate

xds - package for visualizing anatomical and functional images, statistical maps, MR signal vs. time, etc.

Each tool is described in detail in the Appendix – "Software Tools" at the end of this handout.

Guidelines for Laboratory Report

Your laboratory report should contain answers to the questions specified below. Do not repeat the lab instructions and avoid lengthy introductions. Your report should not exceed 4 pages. Conclude your report with a few sentences summarizing what you learned in the lab.

Part I: Cardiac Gating

This part of the Lab is designed to give you a physical feeling for data acquired with and without cardiac gating. Many of the analyses you will perform parallel those of Guimaraes et al. (1998), so you may find their paper useful in completing this part of the Lab.

Specific Instructions:

To get started, type

    attach hst.583
    cp -r /afs/athena.mit.edu/course/other/hst.583/lab_data/lab3 .

Directory *Lab3.1* contains two sets of functional images (*A.bshort* and *B.bshort*). Both were acquired using a standard fMRI block paradigm, i.e. a stimulus (orchestral music) was repeatedly turned on for 30 sec and off for 30 sec. For both sets of data, a single slice was imaged which passed through the inferior colliculi and Heschl's gyri (Figure 1). One data set was acquired using a fixed TR (= 2 sec). The other data set was acquired in the same experiment using cardiac gating. In this case, the subject's electrocardiogram was measured and used to trigger the scanner. Images were acquired every other heart beat (Figure 2) so that the TR would be approximately the same as for the "fixed TR" data set (i.e., ~2 sec; Note that a typical heart rate is ~60 beats/ min = 1 beat/sec). Directory *Lab3.1* also contains files *A.para* and *B.para* with information on the experimental paradigm. Specifically, they contain a code for each successive functional image in *.bshort. The code indicates whether an image was acquired during the "stimulus on" condition (1) or the "stimulus off" condition (-1).
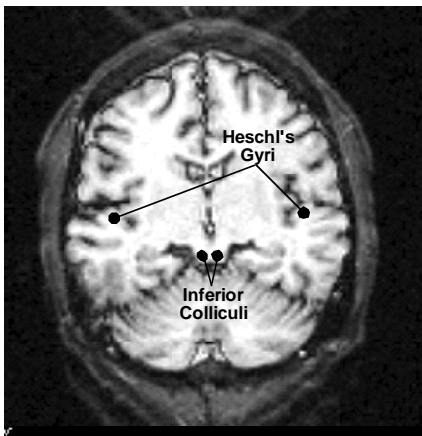
Figure 1: T1-weighted anatomical image of the functionally imaged slice.
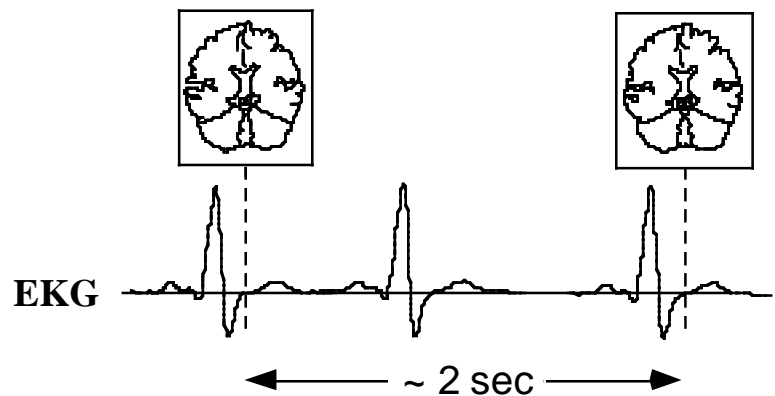
Figure 2: Timing of image acquisitions relative to EKG during cardiac gating.

The files *LeftIC_lowres.ovl*, *RightIC_lowres.ovl*, *LeftHG_lowres.ovl* and *RightHG_lowres.ovl* in *Lab3.1* contain the coordinates of voxels overlaying the inferior colliculi and Heschl's gyri. These overlay files will be used below to locate the

anatomical structures of interest on the low resolution functional images. You can use another set of overlay files (*_hires.ovl) to locate these structures on a high resolution anatomical image (*HiRes.bshort*) of the functionally imaged slice using xds:

    xds -z3 -b HiRes.bshort &
    cp LeftIC_hires.ovl default.ovl
    place cursor in the xds window and hit "o" to display default.ovl file on the image
    cp RightIC_hires.ovl default.ovl
    …

Question:
    I.1 - Compare the two data sets quantitatively using the *standard_deviation* program and provided *_lowres.ovl files:

    standard_deviation -i A.bshort -p A.para -o A.stdev.bfloat
    standard_deviation -i B.bshort -p B.para -o B.stdev.bfloat
    xds -z3 A.stdev.bfloat &
    cp LeftHG_lowres.ovl default.ovl
    place cursor in the xds window and hit "o"
    hit "s" to display statistics of the selected *.ovl file

    …
    You may also want to examine plots of image signal vs. time for different voxels using *xds*, or play a "movie" of images using *xds*. Which data set was acquired using a fixed TR, and which with cardiac gating? Explain your reasoning.

    Directory **Lab3.1** also includes the file *Intervals*. This is a text file containing the time interval (in msec) between each successive pair of image acquisitions in the gated data set. Heart rate fluctuates, so the time interval between acquisitions is not constant. This non-constant interval results in fluctuations in signal because of the uneven recovery of longitudinal magnetization from acquisition to acquisition. Correct the data for this effect using the *gating_correction* program.
    Questions:
    I.2 - Summarize the most salient aspects of the correction algorithm (described in Guimaraes et. al., 1998).
    I.3 - Check whether the gated data were truly corrected by comparing the pre- and post-correction data. Explain why you think it was (or wasn't) corrected.
    I.4 - Quantitatively compare the fixed TR and gated/corrected data for (a) auditory cortex, and (b) the inferior colliculus. (use the *_lowres.ovl files provided and the *standard_deviation* program). Explain any differences between cortex and inferior colliculus.
    I.5 - Was cardiac gating worth the added experimental complexity? Compare activation maps calculated using fixed (*FixedTR.t.bfloat*) and gated/corrected (*Gated.t.bfloat*) data sets.

    xds -z3 -b -A FixedTR.t.bfloat HiRes.bshort
    xds -z3 -b -A Gated.t.bfloat HiRes.bshort
    These color-coded activation maps indicate the p-value result of a statistical test applied to each voxel of the imaged slice (red and yellow correspond to the lowest ($p = 0.01$) and highest ($p = 2 \times 10^{-9}$) significance levels, respectively). The statistical test was a t-test which compares the mean image signal during stimulus "on" conditions to the mean signal during stimulus "off" conditions.

Part II. Experimental design using Clustered Volume Acquisition (CVA)

Part IIa: Combining CVA with Cardiac Gating

Animal work has shown that the representation of sound in neural firing patterns changes considerably from brainstem to cortex. Suppose you want to examine these changes in humans using fMRI. In other words, you want to sample activation in the various auditory cortical areas that cover the superior temporal lobe (i.e. use multislice imaging) and, simultaneously, detect activation in subcortical auditory structures. This can be accomplished by combining cardiac gating (to optimize detection of brainstem activation) with CVA (to avoid the contaminating effects of the gradient noise). This part of the Lab considers issues related to combining these two techniques.

Specific Instructions:

Directory **Lab3.2a** contains a functional image data set (*CVA_0{00-10}.bshort*) acquired using cardiac gating and CVA with a long TR. In this case, 11 slices were imaged in a cluster lasting 800 msec (Figures 3, 4). The acquisition of this 11-slice volume was synchronized to the subject's EKG. A volume was acquired approximately every 8 sec. The intervals between each consecutive pair of volume acquisitions for this data set are in **Lab3.2a**/*Intervals*. The experimental paradigm is coded in CVA.para.
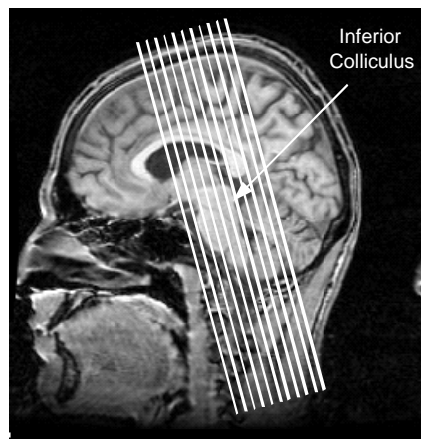
**Figure 3:** Imaged slices superimposed on a sagittal anatomical image located near the midline.

Figure 4: Timing of image acquisitions relative to the subject's EKG for the functional image data in directory Lab3.2a.

Questions:

II.1 - Slice *CVA_004.bshort* intersects the inferior colliculi. Correct the data for fluctuations in the subject's heart rate using *gating_correction*. Quantitatively compare signal variability in the inferior colliculi before vs. after correction using *standard_deviation* and *CVA.para* (use *LeftIC_lowres.ovl* and *RightIC_lowres.ovl* in **Lab3.2a**). Does the effect of the correction (or lack thereof) make sense? Why? Does this result imply anything about the usefulness of cardiac gating in long TR experiments?

II.2 – Consider a subject with a heart rate that varies between 75 and 85 beats/min. Suppose you are imaging this person using CVA and cardiac gating (TR ~8 sec). The image cluster duration is 800 ms. The delay from the time the scanner is triggered by the EKG to the beginning of the cluster is D = 150 ms (see Figure 4).

Consider two possible orders of image acquisition illustrated in Figure 5. In one, images are acquired sequentially within a cluster from anterior to posterior (A). In the other, they are acquired from posterior to anterior (B). To ensure that the slice containing the inferior colliculi is truly cardiac gated, which slice order would you use? Why? You may want to draw a picture similar to the one above illustrating the timing of image acquisitions relative to the subject's electrocardiogram.
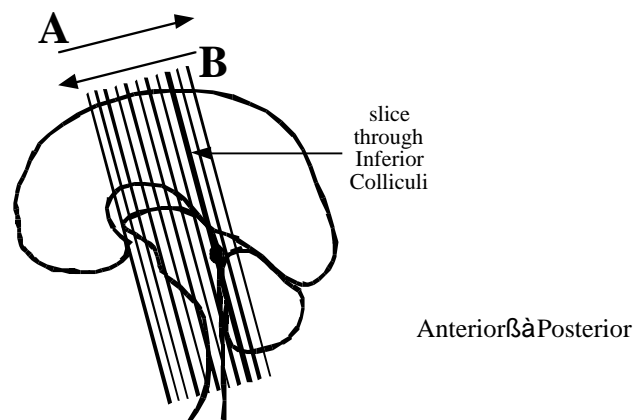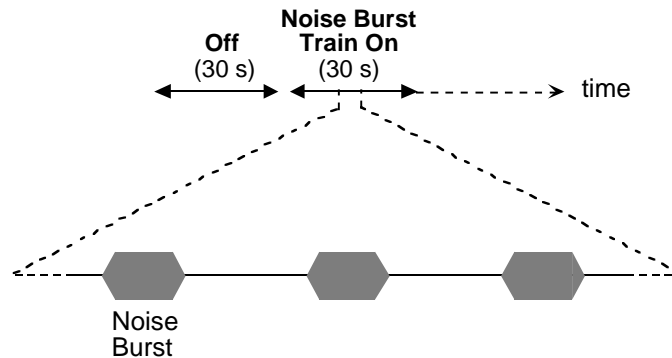

Figure 5.

Part IIb: CVA and temporal sampling

While the contaminating effects of acoustic scanner noise can be reduced using CVA with a long TR (e.g., 8+ sec), the price is diminished temporal resolution. This part of the lab (a) illustrates a potential pitfall of this lower temporal resolution, and (b) examines ways this pitfall can be avoided by controlling the timing between image acquisitions and the auditory stimulation paradigm.

To begin, you will examine the time course of activation in auditory cortex at high temporal resolution (~2 sec) for two example sounds. You will then consider the implications of sampling these time courses at a lower temporal resolution. The example sounds were trains of repeated noise bursts (a stimulus commonly used in auditory neurophysiologic and psychoacoustic investigations). The "noise" of each burst sounds like the static from a radio that is not tuned to a station. For one sound, bursts occurred in a train at a low rate (2/sec). For the other, the rate was high (35/sec). Each burst was ~25 ms long.

Figure 6. Experimental paradigm

Specific Instructions:

Directory **Lab3.2b** contains two functional image data sets (*LowRate.bfloat* and *HighRate.bfloat*) acquired using cardiac gating (TR ~2 sec), but not CVA. In these cases, a single slice, rather than multiple slices, was imaged in order to reduce the effects of acoustic scanner noise without sacrificing temporal resolution. The slice passed through the inferior colliculi and Heschl's gyri. *LowRate.bfloat* was acquired using low-rate trains of noise bursts as the stimulus, and *HighRate.bloat* was acquired using high-rate trains of noise bursts as the stimulus. These data have already been corrected for variations in signal due to the variations in the subject's heart rate using *gating_correction*. They have also been interpolated to a constant TR=2s for the purpose of averaging described below. Both data sets were acquired in a block paradigm, i.e. the noise burst train was repeatedly turned on for 30 sec and off for 30 sec (Figure 6). The total duration of image acquisition for each stimulus was ~9 min. Notice, however, that each functional data set contains only 35 images because the data were divided onto 70 sec.-long blocks of time (with 10 sec overlap) and, then, these blocks were averaged. Specifically, the first five images correspond to the off condition, the next fifteen images to the stimulus "on" condition, and the remaining fifteen images to the stimulus "off" condition.

Lab3.2b also contains maps of activation to high-rate and low-rate noise burst trains (i.e., *LowRate.t.bfloat* and *HighRate.t.bfloat*). These activation maps were calculated using a t-test to compare image signal during train "on" and "off" conditions. You can see the maps superimposed on an anatomical image of the functionally imaged slice by typing:

    xds –z3 -b -A LowRate.t.bfloat HiRes.bshort &
    xds –z3 -b -A HighRate.t.bfloat HiRes.bshort &

Question:
II.3 - Compare the activation detected in auditory cortex for low- and high-rate trains. Describe the similarities and differences.

You can also display the activation maps on the functional images by typing:

    xds –z3 -A LowRate.t.bfloat LowRate.bfloat &
    xds –z3 -A HighRate.t.bfloat HighRate.bfloat &

File *LowRateStim_lowres.ovl* in **Lab3.2b** contains the coordinates of voxels that showed activation on Heschl's gyrus to low rate noise bursts. Use *xds* to examine image signal vs. time averaged across these voxels for *LowRate.bfloat* and *HighRate.bfloat* (see xds manual in Appendix).

Questions:
II.4 - Draw the time course of the response to low- and high-rate noise bursts. Include an indication of the sound on period. Describe the similarities and the differences between the time courses for the two stimuli. Note that the stimulus goes on at image #5 and goes off at image #20 (Images are numbered from 0 to 34.) Given these time courses, explain the cortical differences in the activation maps for low- vs. high-rate noise bursts.

II.5 - Suppose you were to use CVA with a long TR to examine the activation for 2/sec and 35/sec noise bursts. To best detect activation, how would you time your volume acquisitions relative to the stimulation paradigm? Explain. For simplicity, assume a fixed TR of 10 sec (i.e., no cardiac gating). Also assume a stimulation paradigm as in the above example (i.e. the noise burst train is turned on and off every 30 sec).

The data for 2/sec and 35/sec noise burst trains indicates that certain attributes of sound (e.g., repetition rate) are represented in the time course of fMRI activation. Suppose you want to understand how this representation varies across auditory cortical areas. You would need to measure activation with high temporal resolution in multiple slices while minimizing the effects of acoustic scanner noise.

Question:
II.6 - Design an experiment that uses CVA with a long TR (10 sec), but allows the reconstruction of activation time courses with high temporal resolution (e.g., 2 sec). What is the "cost" (if any) of your proposed approach?

Appendix: Software Tools

In this laboratory, you will use a package called *xds* to visualize anatomical and functional images, statistical maps and MR signal vs. time. You will use a program called *standard_deviation* to generate maps of the standard deviation of image signal over time, and a program called *gating_correction* to adjust for variations in image signal due to the heart rate fluctuations. These functions are executables of C programs and can be run from the command line in the Athena environment. The programs are explained in more detail below:

standard_deviation

Usage: standard_deviation -i inputfile.bshort -p paradigm.para -o outputfile.stdev.bfloat
Generates a file outputfile.stdev.bfloat that contains two maps:

       1st map is the standard deviation during stimulus ON conditions for every voxel
       2nd map is the standard deviation during stimulus OFF conditions for every voxel.

For each voxel and condition, the standard deviation is calculated as follows:

$$\text{standard deviation} = \sqrt{\frac{\sum_{i=1}^{N}\left(S_i - \frac{\sum_{i=1}^{N}S_i}{N}\right)^2}{N-1}}$$

       where S_i is the signal for the ith image and N is the number of images in the condition.

       We calculate the standard deviation for the "ON" and "OFF" conditions separately so that signal variability estimates are not obscured by changes in signal corresponding to activation. The paradigm.para file contains information about which images where acquired during ON conditions ("1") and which images were acquired during OFF conditions ("-1").

gating_correction

Usage: gating_correction -i inputfile.bshort -F Intervals -o outputfile.corr.bshort
Generates a file outputfile.corr.bshort in which image signal is corrected to the value it would have had if the interval between image acquisitions had been fixed (see Guimaraes et. al, 1998) by using the text file *Intervals* which contains the time between each successive pair of image acquisitions. The size of the output file is the same as the size of the input file.

       Note: Both **standard_deviation** and **gating_correction** are sensitive to the input/output file type. Therefore, use file extensions (.bshort, .bfloat) as demonstrated above.

xds

Usage: xds [-options] inputfile(s) &
Options:

       -A   display activation map (e.g. p-value map)
       -z   define size of the window displayed (e.g. z3)
       -b   perform a bilinear interpolation on input file(s)

Using the mouse:

       - Left button is used to select voxels for inclusion in a region of interest (ROI)
       - Middle button is used to change contrast (hold it down and move the mouse horizontally) and brightness (move vertically)
       - Right button is used to display a time-series of images in a movie-like fashion.

<u>Displaying signal vs. time:</u>

- Place the cursor in the image window and hit "g". A new window will appear containing a plot of image signal vs. time at the location of the cursor. If you move the cursor to different locations in the image window, you will see the signal vs. time plot update for each new location.

- Hit "N" to toggle between "full range with standard deviation" and "local scale with no standard deviation" modes.

- Click on a particular place in the signal vs. time window to display a corresponding image in the image window. Alternatively, type an image number (from 0 to N-1) and hit "enter". Image numbers are displayed in the lower left corner of the image window.

<u>Obtaining image statistics:</u>

- Select an ROI by either
    - Using the left mouse button
    - Loading voxel coordinates from the default.ovl file by hitting "o"
- Hit "s" (statistics will be displayed in the command window)
- Hit "O" to save an ROI into default.ovl (copy default.ovl into filename.ovl after)
- Hit "C" to clear (i.e. delete) an ROI from the image window