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HST.583 Functional Magnetic Resonance Imaging: Data Acquisition and Analysis
Fall 2008

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HST.583 Problem Set #4- Statistical Analysis of fMRI Data
November 12, 2008

1. Group GLM. Given the following table [table TBD]:

	Diagnosis	Age	HRF
Subject 1	Normal	42	2.87
Subject 2	Normal	43	-1.56
Subject 3	Normal	32	-1.42
Subject 4	Schizophrenic	41	1.58
Subject 5	Schizophrenic	43	0.57
Subject 6	Schizophrenic	39	-2.19

a. Write out the design matrix that models the effect of age and diagnosis. Do not assume that the slope between HRF amplitude and age is the same across diagnosis.

[

```
     1    42     0     0
     1    43     0     0
     1    32     0     0
     0     0     1    41
     0     0     1    43
     0     0     1    39
```

The columns can be swapped]

b. Write out the contrast matrix that tests for the effect of diagnosis on the intercept.

atrix, then contrast matrix columns must be swapped.

c. Write out the contrast matrix that tests for the effect of diagnosis on the slope.

atrix, then contrast matrix columns must be swapped.

d. Write out the design matrix that models the effect of age logarithmically instead of linearly.

[Same matrix but the age is replaced by log(age)

```
    1.0000    3.7377         0         0
    1.0000    3.7612         0         0
    1.0000    3.4657         0         0
         0         0    1.0000    3.7136
         0         0    1.0000    3.7612
         0         0    1.0000    3.6636
```

]

2.
a) What does it mean for a design matrix to be singular?

[The design matrix is not of full rank. Equivalently, it has a zero determinant. Also equivalently, at least one column of the matrix is an exact linear combination of the other columns.]

b) What does it mean for a design matrix to be ill-conditioned?

[The determinant is nearly zero; at least one column is nearly a linear combination of the other columns.]

c) What are the implications of a) and b) above on:
i) the ability of the model to fit the data?
[None. Poorly conditioned design matrices impact the interpretation of the coefficients of the model; the model fit is unaffected.]

ii) the coefficient estimates and their standard errors?
[The coefficients are not uniquely determined for the situation where the design matrix is singular, and hence they have infinite standard errors. For the poorly-conditioned situation, the large uncertainty in the coefficients will result in large standard errors for at least some of the coefficients.]

3. What is the difference between a fixed-effects and a random-effects model?

[In a fixed effects model, the overall mean activation for each subject is a constant, which is estimated from the data. So each subject has a coefficient associated with it in the GLM which is that subject's mean. In a random effects model, the subjects are modeled as a random sample of subjects from a population. Hence, it is usually not meaningful to estimate the 'mean' activation for a subject, since this is a realization of a random variable, not an unknown constant. Consequently, the random effect for subject is assumed to be a Gaussian random variable with mean zero, and it is characterized by it's variance: the between-subject variance.

Fixed effects models are appropriate when one does not wish to generalize beyond the subjects at hand, or when it is perhaps hopeless to consider doing so because there are too few subjects to reasonably expect to be able to estimate between-subject variability.

Random effects models yield results that are likely to be valid for future subjects sampled from the same population. Hence, random effects models are usually preferred in fMRI analysis.]

Can one have a model that includes both types of effects?
[yes]

4. Is there an optimal level of spatial smoothing. If not, why? If so, what is it?

[Yes. It should be the same size as the activation blobs you are looking for.]
[No. There is no one level of smoothing that is optimal as the optimal size depends on the size of the activation blobs, which will differ across space, contrast, and subject]
[Yes. The minimum amount necessary in order for Gaussian random field theory to be valid].

5. Sketch out a typical hemodynamic response function (HRF), give approximate values for the onset delay, delay to peak, and equilibration time.

[ ]

7. You are performing an experiment in which you are manipulating a psychological variable (eg, working memory load) at levels of 1, 3, and 5 (ie, you are presenting stimuli that represent levels 1, 3, and 5). You wish to test for a linear effect of the variable. There are two possible ways: (Method 1) you can model the level directly in the design matrix, or (Method 2) you can model each level separately and test for a linear effect with a contrast. For the purposes of this exercise assume a shape to the hemodynamic response and do not worry about nuisance variables like offset and drift.

a) Describe in words how you would implement Method 1. Include a contrast matrix to test for the slope.

[There would be two regressors in the design matrix. One regressor would be the regressor created from the design when all levels were pooled into one condition. The other would be the same except that each individual presentation is scaled by its level. The first regressor codes for an offset and the second codes for the slope of the effect. The contrast would be [0 1].]

b) In Method 2, you would have a regressor for each level. Describe how you would create a contrast matrix to test for a non-zero slope.

[This is set up like another GLM type of problem. You have an independent variable (the levels) and you have observations/dependent variables (the regression coefficients (betas), and you are going to model their relationship by a slope and offset, and then test the slope.

Set up the forward model:

Beta = D*q, where Beta are the HRF amplitude estimates from the 1st level analysis (ie, Beta = [beta1 beta2 beta3]'), D is the linear relationship:

$$D = \begin{matrix} 1 & 1 \\ 1 & 3 \\ 1 & 5 \end{matrix}$$

First column codes offset, 2nd column codes slope, which are the things we want to estimate (ie, q = [offset slope]'). Solve for q = inv(D'*D)*D'*beta. We are only interested in the slope = [0 1]*q = [0 1]* inv(D'*D)*D'*beta. The contrast matrix is the thing we multiply by beta, so C = [0 1]* inv(D'*D)*D']

8. a) What is a null hypothesis?

[The null hypothesis is the situation which obtains if the effect being tested is not true. It usually is of the form of something being equal to zero, for example 'the mean difference in activation between stimulus blocks and fixation blocks is zero'. The logic of statistical hypothesis testing is to tentatively assume that the null is true, to assess the likelihood that this is the case via a test statistic, and then to (hopefully) reject the null in favor of the alternative if this likelihood is sufficiently small. The null hypothesis can either be rejected or not rejected; it can never be accepted.]

b) What is an alternative hypothesis?

*[The alternative hypothesis is the situation which one assumes will obtain if the null is not true. Situations not included in either the null or the alternative are assumed a-priori to be *impossible*.]*

c) Give an example of how one can have two different p-values for the same null hypothesis depending on the alternative hypothesis which is used (hint: these two p-values for a simple example of this situation will have ratio 1/2).

*[If one tests the null hypothesis that a coefficient is zero against the alternative that it is positive, then one will obtain some p-value, say "p". If one performs the same test with the same data but tests against the alternative that the coefficient is *nonzero*, then one will obtain the p-value "2p". The first is called a one-tailed test, the latter a two-tailed test.]*

d) Can both the null and the alternative hypothesis be true for a valid hypothesis test?

[No.]

9. What is the problem of multiple comparisons? Choose one solution to explain.

[Consider the situation where a single hypothesis is tested at the 0.05 significance level. This means that if one were to imagine repeating the experiment many times, and if this null hypothesis happened to be true, then one would make a mistake by rejecting this hypothesis only 5% of the time, due to chance. Now if one imagines testing 20 such hypotheses at the same time, and if these hypotheses, for simplicity, happen to be independent, then one would make a mistake on average once for each replication of the experiment, not 1 in 20 as before. An example is hypothesis tests at each of thousands of voxels.]

10. a) Why is it desirable to specify regions of interest in an fMRI experiment before looking at the data, to the full extent that this is possible?

[Selecting regions a-priori reduces the problem of multiple comparisons and thus can greatly increase the power of hypothesis tests and enhance the likely validity of conclusions. Selecting regions of interest a-posteriori means that the same data that are used to formulate hypotheses are being used to test the hypotheses.]

b) If a region that was not of interest *a-priori* is found to have a statistically significant p-value once the data are analyzed, what can one say about the interpretation of this p-value?

[The p-value overstates the statistical significance of the result, by an unknown amount. The extent to which the p-value overstates the significance depends on to what extent hypotheses are selected a-posterior (i.e., how much "fishing" is being done.).

c) What can be done to improve the situation in b) above?

[Conduct a follow-up study, for which hypotheses formulated a-posteriori in the first (pilot) study will be specified a-priori. Or else, cross-validate by setting using some subjects (chosen at random) for hypothesis-generation, and setting aside the others for validation. In any case, the fact that the regions were not of a-priori interest needs to be made clear in any report of the results.]