

Solving the multiple comparison problem in fMRI using a method based on bootstrapping the Order Statistics of the resting state data

R. R. Nandy¹, D. Cordes¹

¹Department of Radiology, University of Washington, Seattle, Wa, United States

Introduction

The multiple comparison problem is relevant when we have a family of hypotheses $\{H_\omega: \omega \in \Omega\}$ at voxel ω . In fMRI, Ω stands for the collection of all intracerebral voxels. The omnibus null hypothesis H_Ω is the hypothesis of no activation anywhere in the brain. Clearly this hypothesis is rejected as soon as a single H_ω is rejected. Suppose we want to test the omnibus hypothesis at a level α . If we test every individual H_ω at the same level, the probability of incorrectly rejecting at least one H_ω is much larger than α . Or in other words, in such a test procedure, the omnibus hypothesis is really tested at a higher value than originally assigned. This implies that the p -value for each individual test needs to be adjusted to test the omnibus hypothesis. Two popular methods to account for multiple comparison are the Bonferroni correction, which is too conservative and the Gaussian random field approach, which makes too many assumptions. Here we propose a method based on bootstrap techniques applied to the *order statistics* of the resting state data (which can be considered to be null data) to generate resamples of the order statistics and then calculate the distribution of the maximum statistic to account for multiple comparison. This method is extremely versatile and may be applied to any test statistic with a known parametric distribution. In fact, in most cases, the method is applicable even when the distribution is unknown or computationally intractable.

Theory and methods

Let the test statistic at voxel ω be denoted by Y_ω . For any threshold u for the test statistic, we want to calculate the probability of incorrectly rejecting the omnibus hypothesis H_Ω (rather than the individual hypotheses H_ω). By changing sign of the test statistic if necessary, without loss of generality, it can be assumed that a voxel is declared to be active when the test statistic is larger than the threshold. Then we can write

$$P[H_\Omega \text{ is rejected incorrectly}] = P[H_\omega \text{ is rejected incorrectly for some } \omega \in \Omega] = P[(Y_\omega > u) \text{ for some } \omega \in \Omega] \\ = P[\bigcup_{\omega \in \Omega} (Y_\omega > u)] = 1 - P[\bigcap_{\omega \in \Omega} (Y_\omega \leq u)] = 1 - P[\max_{\omega \in \Omega} Y_\omega \leq u] = P[\max_{\omega \in \Omega} Y_\omega > u].$$

The corresponding probability is the Familywise Error Rate (FWE). We now describe how to estimate the distribution of $\{\max Y_\omega\}$ using bootstrap applied to the k largest order statistics $\{Y^1, \dots, Y^k\}$. Although the method may be applied to a broad class of test statistics, it is preferable to make a transformation of the test statistic, if the parametric distribution of the test statistic is known. We calculate the negative logarithm of the p -value corresponding to the test statistic to obtain our transformed variables. Due to the monotonicity of the transformation, without loss of generality, we can assume that Y is already transformed. Define $\{d_i = i(Y^i - Y^{i+1}), i=1, \dots, k\}$ as normalized sample spacings for the k largest order statistics. If the observed samples at the voxels are i.i.d, then so are the normalized sample spacings [1]. This is true since the transformed test statistic is an exponential random variable. In the present context, the samples are not independent, but we make that assumption anyway. This does not have a strong adverse effect on the result since k is chosen to be very small compared to the total number of voxels, whereas in the Bonferroni method, all the voxels are assumed to be independent. Furthermore, this method can be refined even further to address the dependence issue, but will not be discussed here. The k largest order statistics can be expressed as a linear function of normalized sample spacings and Y^{k+1} as follows.

$$Y^j = Y^{k+1} + \sum_{i=j}^k i^{-1} d_i, \quad j = 1, \dots, k.$$

Since $\{d_i, i=1, \dots, k\}$ are i.i.d, we can use bootstrap to obtain resamples of normalized spacings $\{d_i^*, i=1, \dots, k\}$ which can be used to generate resamples $\{Y^{*1}, \dots, Y^{*k}\}$ of the k largest order statistics from which the distribution of $\{\max Y_\omega\}$ can be obtained empirically. Since resting state data is considered to be null, the obtained distribution can be considered to be the null distribution of $\{\max Y_\omega\}$. This method may still be applicable when the transformation of the test statistic is not possible due to a lack of knowledge of its distribution. It can be shown that under certain regularity conditions, for a suitably chosen k , the normalized spacings are i.i.d. asymptotically [2]. Due to the large number of voxels in consideration, the asymptotic result is applicable in most cases.

Results

As an example we consider the activation map obtained from a periodic phoneme matching task using a single convolved boxcar function with a delay of 6 sec. Resting state data with an identical EPI protocol is also acquired for the bootstrap procedure. In Figure 1, we have plotted the estimated density function for $\{\max Y_\omega\}$. In Figure 2a & b, we have plotted activation maps corresponding to an adjusted p -value of 0.05 using Bonferroni correction and the proposed method, respectively, for one slice. The chosen value for k is 30 for the bootstrap. The numbers of total voxels detected to be active in the whole brain (14000 voxels) are 297 and 434, respectively. For an adjusted p -value of 0.01, the corresponding numbers are 226 and 367. This indicates that the proposed method is a significant improvement over Bonferroni correction. It is also known that FWE obtained using Gaussian random field approach is usually not a vast improvement over Bonferroni due to the various assumptions made on the smoothness of the data. If the conceptual and computational simplicity of the proposed method is taken into consideration, this method may prove to be an improvement over all existing methods to control the FWE.

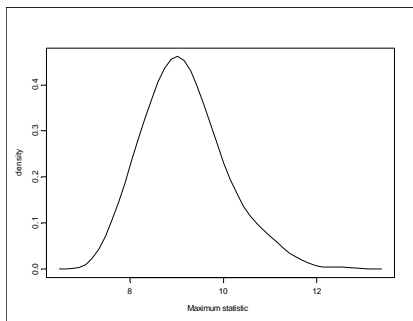


Figure 1. Distribution of the maximum statistic.

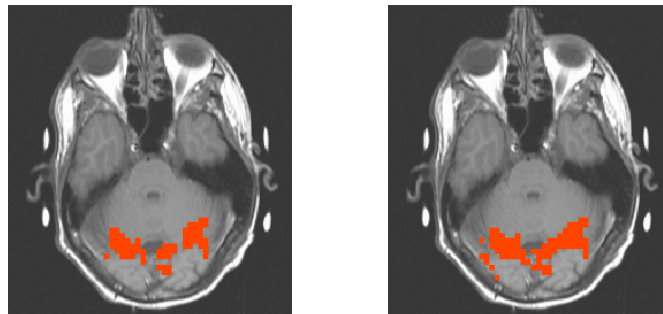


Figure 2a & b. Adjusted activation maps using Bonferroni correction (left) and the maximum statistic (right).

References

1. Pyke, R. *J. Roy. Statist. Soc. Ser. B.* 27: 395-436 (1965).
2. Weissman, I. *J. Amer. Statist. Assoc.* 73: 812-815 (1978).