# A novel activation threshold selection for fMRI data using order statistics

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**Introduction:**

An important consideration in constructing the activation map for an fMRI dataset is to choose the right threshold. In a parametric approach, typically a pre-assigned p-value is chosen as the threshold. However, in fMRI, it is necessary to make a few corrections to obtain an adjusted p-value. First, the voxel timecourses usually have high temporal autocorrelation and it is necessary to estimate the temporal autocorrelation structure to obtain the p-value. SPM2 uses an ReML approach to address this problem [1]. The second problem is known as the multiple comparison problem, which arises from the fact that we are testing the same hypothesis at tens of thousands of voxels and the probability of at least one voxel being detected to be active incorrectly is much larger than the single-voxel p-value. The simplest way to address this problem is to use the Bonferroni correction, but this approach is too conservative considering the spatial dependence in the fMRI data. A more popular method which utilizes the spatial smoothness of the data is based on the theory of Random Fields (RFT) and is implemented in SPM2. However, both of these corrections have certain weaknesses. It has been established that even resting-state data has some low frequency behaviors [2] and there is a reasonable chance that there is some overlap between the inherent low frequencies in the brain and the paradigm frequency. Unfortunately, even a standard high-pass filter cannot eliminate the low frequencies matching the paradigm since the cutoff is half the frequency of the actual paradigm. As a result, it is not unusual to have decent "activation maps" with resting-state data when SPM2 is implemented. Regarding the RFT approach to the multiple comparison problem, it is imperative to use spatial smoothing to implement the RFT. Furthermore, even when spatial filter is used, the estimates using RFT is often no better than Bonferroni. We extend a previously proposed semi-parametric method using order statistics to overcome the problems mentioned above [3]. The proposed method is more parametric and will have several advantages over the previous method and other conventional approaches; (i) the correction for temporal autocorrelation is not required, (ii) resting state data is not required, (iii)resampling is not required and (ii) it indeed offers a threshold better than Bonferroni even without any spatial filter.

**Methods**:

Ideally, one should use resting state data as null data and the observed values of the test statistic at all voxels as the observations $X_i$. In the absence of resting state data, one can simply use same number of new regressors as the true regressors but orthogonal to the true regressors. With respect to the new regressors, even the activation data can be considered null. To adjust for the multiple comparison, it is necessary to estimate the distribution of the maximum value of the statistic used in the analysis over all voxels under null data [3]. Define $d_i = i(X^{(i)} - X^{(i+1)}), i = 1,...,k$ as the normalized sample spacings for the $k+1$ largest order statistics $X^{(i)}$ from the null data. A straightforward analytic calculation shows that if the observations are i.i.d. exponential, so are the normalized spacings. However, the observed values $X_i$ are not exponential in general. To solve the problem, let $Z_i$ be the corresponding *p*-value using the parametric distribution. If the parametric distribution is accurate, the function $-\log(Z_i)$ is exponentially distributed since $Z_i$ is uniformly distributed. In the following, without loss of generality, we can assume that $X_1,..., X_N$ are already transformed using the log transform. Now, for any $k$, $X^{(1)} = X^{(k+1)} + \sum_{i=1}^{k} i^{-1} d_i$ is the maximum. Since the spacings are i.i.d. exponential and $X^{(k+1)}$ is known, the distribution of maximum can be easily calculated. It should be noted that if the parametric distribution is accurate, the exponential decay parameter is 1 and need not be estimated. But, in reality, the parametric distribution is not accurate in general (primarily due to imprecise whitening of correlated noise). Hence we estimate the decay parameter $\lambda$ simply by taking the mean of the normalized spacings. This provides a more accurate estimate of the distribution. The method is not purely parametric, since the distribution is not independent of the data, which is usually the case in a purely parametric formulation. It is important to note that though $\{d_1,...,d_k\}$ may not be strictly independent with some underlying structure, the method is still expected to work due to the following reason. The underlying structure can only restrict the maximum from being too large (the maximum would be larger statistically if all voxels are independent). This in effect makes the tail of our estimated distribution heavier. Hence the estimated FWE using this method will still be an upper bound and if $k$ is not too large, there will still be considerable improvement over the Bonferroni estimate. We choose $k$ to be 100, which is small enough compared to the number of voxels and large enough for a robust estimation of $\lambda$. One simple way to make the estimated threshold more robust is to estimate the threshold for several successive choices of $k$ and then take the average.

**Results:**

An event-related design is a fair basis for the comparison of thresholds obtained using Random Field approach and our proposed method, since there is usually little low frequency effect. Since the parametric threshold does not depend on the actual regressor, the adjusted t-threshold is again 4.68 at 0.05 p-value. We analyzed the same resting-state dataset for ten different event-related paradigms. The onsets of the events for each paradigm were determined randomly from a Poisson distribution with mean 20 seconds. A constraint for a minimum separation of 6 seconds between two successive events was implemented. Since there is no strongly dominant frequency, there was no false positive at this threshold for any of the 10 paradigms. The estimated t-threshold using our method after taking averages over the 10 paradigms is only 4.21 which is significantly lower than the parametric threshold. Again, no false positive is obtained at this threshold.

**Conclusion:**

We have presented a novel scheme for estimation of the FWE or a properly adjusted threshold to address the multiple comparisons problem in fMRI as well as the inherent low frequency processes in the resting brain. The proposed methods are easy to implement and are not costly computationally. The methods can be applied broadly to almost any relevant test statistic in fMRI, even when the parametric distributions are unknown or too complex to calculate. We believe that the new methods will be beneficial for the fMRI community.

**References:**

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