Variability of Spatial Location of Activation in fMRI and PET CBF Images

L. MA, K. J. WORSLEY, A.C. EVANS

Department of Mathematics and Statistics and McConnell Brain Imaging Centre, Montréal Neurological Institute, McGill University, Montréal, Québec, Canada. E-mail:ma@math.mcgill.ca

Introduction

Most statistical analysis of fMRI and PET CBF data is concerned with the *detection* of local activation. In this abstract, we propose two theoretical methods for assessing the *variability* of the spatial location of these activations, once they are detected. The methods use random field theory[1] to give approximate standard errors and confidence intervals for the spatial location of the activation.

Overall spatial error can be broken down into three components as follows:

$$\text{Spatial error} = \text{Registration error} + \text{Structure error} + \text{Random error}.$$

The first is registration error due to anatomical variability of the underlying structures. This can be reduced by linear brain alignment prior to processing, and it can be eliminated (in principle) by non-linear warping of the brain to an atlas standard. The second is structure/function error due to variability of function within the same structure. For example, function may be located at the fundus, midway up, or on the shoulder of a sulcus. The effect is to blur the response on data averaged across a number of subjects. This source of variability cannot be eliminated by current non-linear warping methods.

The third is random error due to the smoothed random noise added to the true underlying activation signal. This source of error would still remain even if the first two sources of error could be eliminated. Random error is due to the fact that the location of the maximum (signal + noise) is not equal to the location of the maximum signal alone. This source of error will be estimated from random field theory[1] in the Methods section. This opens up the possibility of estimating the structure/function error by eliminating registration error, and subtracting estimated random error from the remaining observed spatial error.

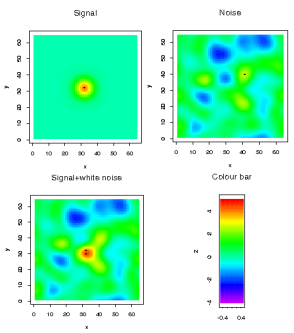

Figure 1: The random error: after adding the noise to the signal, the location of the maximum changes.

Methods

Activation is detected by local maxima of a smooth Gaussian statistical parametric map (SPM$\{Z\}$) derived from the data. We shall assume that the spatial extent of the signal prior to smoothing has a Gaussian shape that matches the point spread function (psf) of the smoothed data. The first theoretical result (the Wald method) is the standard deviation of the spatial location of the peak activation in SPM$\{Z\}$:

$$\text{Standard deviation(peak location)} \approx \frac{\text{FWHM}}{\text{Max } Z\sqrt{4\log_e 2}},$$

where FWHM is the full width at half maximum of the psf, and Max Z is the local maximum of the SPM$\{Z\}$. The second theoretical result (the likelihood ratio method i.e. the L.R. method) is an approximate 3D confidence region for the location of the peak activation:

$$\text{Confidence region(peak location)} \approx \left\{(x,y,z) : Z(x,y,z) \geq \sqrt{(\text{Max } Z)^2 - \chi^2_3(\alpha)}\right\},$$

where (x,y,z) is the coordinates of a voxel in the confidence region, $Z(x,y,z)$ is the value of SPM$\{Z\}$ at that coordinate, $\chi^2_3(\alpha)$ is the upper α point of the χ^2 distribution with 3 degrees of freedom, and $100(1-\alpha)\%$ is the desired confidence. In other words, it is the set of voxels where SPM$\{Z\}$ exceeds the threshold $\sqrt{(\text{Max } Z)^2 - \chi^2_3(\alpha)}$.

Results

The methods were checked by simulation. Gaussian white noise was simulated, a signal was added, and the result was smoothed with a Gaussian psf. Crucial conditions are that the amplitude of the signal is high, the signal shape matches the psf, and the signals are well separated. To investigate the necessity of these conditions, we tried varying the amplitude, width, shape and separation of the signals.

- **Varying the amplitude a:**

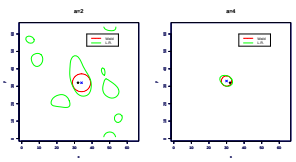

Figure 2: By increasing the amplitude of the signal, the estimated maxima is getting closer to the true maxima and the confidence region of both methods is smaller.

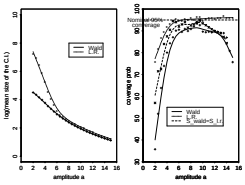

Figure 3: If the signal amplitude is too low ($a < 5$), then the coverage probability of both methods is too small.

- **Varying the width w_x of the signal:**

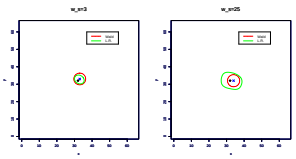

Figure 4: When the width of the signal is smaller, the confidence region is smaller.

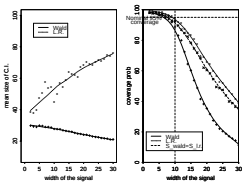

Figure 5: The confidence region has the right coverage when the width of the signal matches that of the psf (10mm).

- **The shape of the signal is a 'box' rather than a Gaussian, and the width varies:**

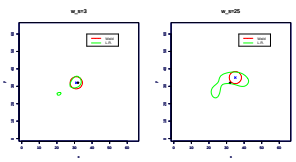

Figure 6: Again, when the width of the signal is smaller, the confidence region is smaller.

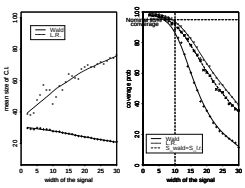

Figure 7: When the signal is defined as a 'box' shape, the results of these two methods are still good.

- **Varying the separation of the signals:**

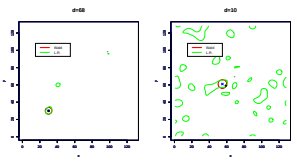

Figure 8: When the separation of two signals is low, the confidence region does not cover the signal maximum.

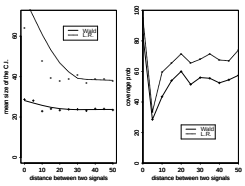

Figure 9: When the signals are very close to each other ($< 5mm$), the coverage probability is accurate; when the seperation is approximately equal to the FWHM of the signal ($\approx 10mm$), the coverage probability is very low; when the signals are well seperated ($> 20mm$) the coverage increases.

Application to PET CBF study

When applied to some typical fMRI and PET CBF data sets, the 95% confidence regions had half-widths of 3–10mm. As an illustration, the methods were applied to a PET CBF study of pain perception[2].

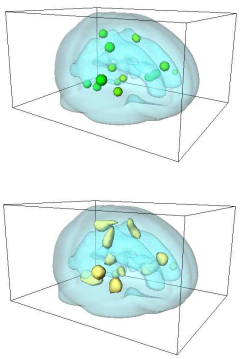

Figure 10: The green areas are 95% confidence region of the Wald method for all local maxima ≥ 4. The yellow areas are 95% confidence region of the L.R. method for all local maxima ≥ 4.

Conclusions

Under the conditions of high signal amplitude, shape matching the psf, and well separated signals, both methods performed equally well, but if these conditions were not satisfied, for example if the signal was wider than the psf, then the Wald method gave a standard error that was too small. However the L.R. method gave a confidence region that was still reasonably accurate, even when the signal had a non-Gaussian shape, for example a 'box' shape. We therefore recommend the L.R. confidence region method.

Reference

1. Adler R (1981) *The Geometry of Random Fields*. Wiley: New York

2. Coghill, RC, Talbot JD, Evans AC, Meyer E, Gjedde A, Bushnell MC, Duncan GH (1994): Distributed processing of pain and vibration by the human brain. *Journal of Neuroscience* 14:4095-4108.