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# Applications of Random Field Theory to Functional Connectivity

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**Abstract:** Functional connectivity between two voxels or regions of voxels can be measured by the correlation between voxel measurements from either PET CBF or BOLD fMRI images in 3D. We propose to look at the entire 6D matrix of correlations between all voxels and search for 6D local maxima. The main result is a new theoretical formula based on random field theory for the *p*-value of these local maxima, which distinguishes true correlations from background noise. This can be applied to crosscorrelations between two different sets of images—such as activations under two different tasks, as well as autocorrelations within the same set of images. *Hum. Brain Mapping 6:364–367, 1998.* © 1998 Wiley-Liss, Inc.

**Key words:** random fields; functional connectivity; correlation

## INTRODUCTION

Functional connectivity between two brain regions is defined as the correlation between pairs of measurements of cerebral blood flow (PET) or blood oxygenation level (fMRI) taken from several scans on the same subject, over several different subjects, or a combination of both.

Two indirect approaches have been suggested for assessing functional connectivity. The first is analysis of correlations between a small number of preselected regions or voxels [Horwitz et al., 1996], or to fit Structural Equations models [McIntosh and Gonzalez-Lima 1994]. Bullmore et al. [1996] have looked at more extensive matrices of correlations between activated voxels, but no thresholding is attempted. More recently, Friston et al. [1997] have used linear models involving interactions with a task. This method looks for the effect of the task on the correlation, such as a change in correlation provoked by the task. Here, we are only interested in the simpler problem of the presence or absence of the correlation.

The second approach is characterization of correlations by a small number of spatial modes, found using a simple Singular Value Decomposition of the scans × voxels matrix [SVD: Friston et al., 1993, SSM: Strother et al., 1995]. To characterize the effects of covariates, several methods have been proposed, all based on an SVD of the covariates × voxels covariance matrix [PLS: McIntosh et al., 1996; SVD-CVA: Friston et al., 1995, MLM: Worsley et al., 1997].

In this article we suggest looking at correlations between all voxels. This involves a very large amount of calculation; for 3D data, the resulting correlation "image" is 6D. The main problem is where to put the threshold in order to screen out null correlations that are due to chance alone, leaving only the most significant correlations that are due to real underlying connectivity. As with other statistical maps, the threshold can

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be set so that the $p$-value of the maximum correlation is controlled at, say, 0.05.

A related problem occurs in linear models for image data with spatially varying covariates. An example is testing for a linear relation between subtracted images from two modalities, such as PET and fMRI. Another example, which we shall use in this study, is testing for a linear relation between subtracted images under two different tasks. In these example, we are relating two images; the usual random field theory [Worsley et al., 1996] only applies to linear relations between one image and *fixed* external covariates (such as age, task difficulty, etc.) which are the *same* for every voxel. We shall show how this problem and the previous problem of functional connectivity are special cases of the more general crosscorrelation field, which we now define.

## CORRELATION FIELDS

### The crosscorrelation field

Suppose that we have $n$ pairs of 3D images. Denote the values of the $i$th pair of images at a 3D voxel with coordinates $(x, y, z)$ by $X_i(x, y, z)$ and $Y_i(x, y, z)$, $i = 1, \ldots, n$. The values are centered over images by subtracting the mean value at each voxel, so that $\Sigma_i X_i(x, y, z) = 0$ and $\Sigma_i Y_i(x, y, z) = 0$. Then the 6D *crosscorrelation field* at "connexel" $(x_1, y_1, z_1, x_2, y_2, z_2)$ is

$$R(x_1, y_1, z_1, x_2, y_2, z_2) = \frac{\sum_{i=1}^{n} X_i(x_1, y_1, z_1) Y_i(x_2, y_2, z_2)}{\sqrt{\sum_{i=1}^{n} X_i(x_1, y_1, z_1)^2} \sqrt{\sum_{i=1}^{n} Y_i(x_2, y_2, z_2)^2}}.$$

This is illustrated in Figure 1D. This field is then searched for local maxima, defined as 6D connexels which have values larger than all 12 neighbors.

### The autocorrelation field

Setting $X_i = Y_i$—that is, crosscorrelating $Y_i$ with itself—produces the 6D *autocorrelation field*, whose values are the correlations between all pairs of voxels of $Y_1, \ldots, Y_n$. This is the statistical map used to assess functional connectivity. Note that voxels separated by less than about one FWHM should be ignored, since they will have high correlation due to the partial volume effect. Note also that only half the remaining voxel pairs should be considered, since $R(x_1, y_1, z_1, x_2, y_2, z_2) = R(x_2, y_2, z_2, x_1, y_1, z_1)$ in this case.

### The homologous correlation field

Setting $(x_1, y_1, z_1) = (x_2, y_2, z_2)$—that is, restricting the crosscorrelation field to its "diagonal" elements (see Fig. 1), produces the 3D *homologous correlation field* whose values are the correlations between $X_{\mathrm{i}}$ and $Y_{\mathrm{i}}$ at the same voxel. This is the statistical map for assessing a linear relationship between $Y_i$ and a spatially varying covariate $X_i$.

### Random field theory

Note that $t$-statistics $T$ for testing for a linear relationship are equivalent to correlations $R$, since $T = \sqrt{n-2}\,\mathrm{R} / \sqrt{1-R^2}$. Hence the homologous correlation field can be transformed into a field that has a $t$-distribution with $n - 2$ degrees of freedom at every point. Curiously enough, even though such a field has a $t$-distribution at every point, it is *not* a $t$-field as defined by Worsley et al. [1996], and so the theoretical results for $P$-values of maximal of $t$ fields cannot be used to assess the $p$-values of maxima of homologous correlation fields.

The problem is quite subtle. The crosscorrelation field can be transformed to a $t$-field if we fix one of the voxels, say $(x_1, y_1, z_1)$. Then we look at the statistical image of all voxels $(x_2, y_2, z_2)$ that correlate with the single fixed voxel. These are the vertical and horizontal lines in Figure 1. This produces the standard *covarying voxel* analysis that has been successfully used by many authors to investigate functional connectivity between a single voxel and all others. In other words, the crosscorrelation field can be transformed to a $t$-field along any "horizontal" or "vertical" line, but not along the "diagonal" (the homologous correlation field) nor in the interior (the cross- or autocorrelation fields). New theoretical results are needed.

If we fix one of the fields, say $X_1, \ldots, X_n$, and regard this as the covariate, then the resulting $t$-statistic field is nonstationary, and the random field theory of Adler [1981] does not apply without serious modification. The way around this difficulty is to make $X_i$ a stationary Gaussian random field, as well as $Y_i$, $i = 1, \ldots, n$. This makes the $t$-statistic field stationary, but it is still not a $t$-field. In fact, it turns out to be slightly rougher than a $t$-field based on a fixed spatially invariant $X_i$, so that its effective FWHM is lower, resulting in slightly higher $P$-values and critical thresholds.

We have extended random field theory to cover the crosscorrelation, autocorrelation, and homologous cor-

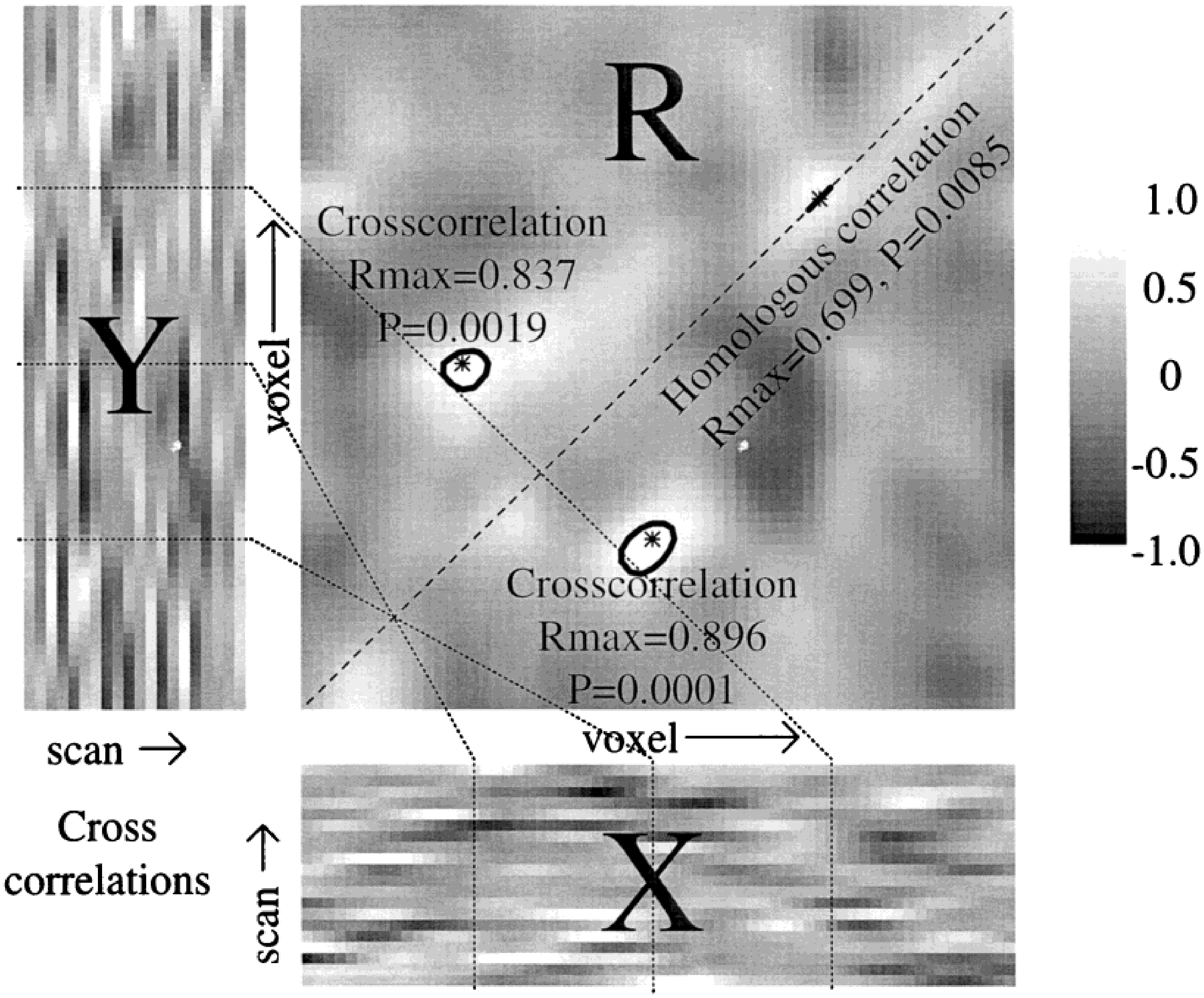


**Figure 1.**

A simulated 2D crosscorrelation field $R$ for $n = 20$ 1D scans, $X$ and $Y$. Dotted lines link the voxels where three simulated positive correlations of 0.85 were added to smoothed white noise. The 1D homologous correlation field is the "diagonal" (dashed line) and the 1D covarying voxel correlation fields for a fixed $X$ voxel are the vertical lines. Local maxima of crosscorrelation and homologous correlation fields are indicated. The previous random field theory can be used for assessing the $P$-value of the maximum of the covarying voxel correlations (vertical or horizontal lines), but new results reported here are required for the 1D homologous correlation field and the 2D crosscorrelation field. Using these results, the $P < 0.05$ threshold contour is shown by thick lines: $R > 0.614$ for the homologous correlation field, and $R > 0.744$ for the crosscorrelation field. The three simulated correlations are all detected at $P < 0.05$.

relation fields to find approximate $p$-values for local maxima searched over regions of arbitrary shape or size [Cao and Worsley, 1998]. The resulting approximate $P = 0.05$ critical thresholds for $n = 40$ images, a 1000cc spherical search region, and 20-mm FWHM smoothing are shown in Table 1, all transformed to a Gaussian scale for easier comparison. Note that the homologous correlation thresholds are slightly higher than the usual $t$-field thresholds for correlations with a single covarying voxel. The auto- and crosscorrelation thresholds are considerably higher due to the higher dimensional search.

## APPLICATIONS

Preliminary analysis of a PET study of 8 subjects $\times$ 6 scans per subject during a vigilance task [Paus et al.,

**TABLE I.** ***P*** **= 0.05 critical thresholds for the maximum correlation of** ***n*** **= 40 images inside a 1000cc spherical search region with 20-mm FWHM smoothing**

| Statistical field | Correlation threshold | Gaussianized threshold |
|---|---|---|
| 3D Gaussian field (for comparison only) | — | 4.16 |
| 3D covarying voxel correlations, $(x_1, y_1, z_1)$ fixed | 0.618 | 4.25 |
| 3D homologous correlations, $(x_1, y_1, z_1) = (x_2, y_2, z_2)$ | 0.648 | 4.52 |
| 6D autocorrelations, $X_i = Y_i$ | 0.799 | 6.18 |
| 6D crosscorrelations | 0.809 | 6.32 |

1997] revealed several autocorrelations that confirmed those already found using a covarying voxel analysis. Homologous and crosscorrelations for subtracted PET images under two cognitive tasks (Petrides et al., in preparation) revealed no significant correlations, probably due to the very small number of images (9). Details of these analyses will be reported elsewhere.

## CONCLUSIONS

This method examines correlations directly, providing a critical threshold above which the correlations are significant. It can be used for any Gaussian image data, such as surface displacements or nonlinear deformations, which might be useful for finding anatomical connectivity, analogous to functional connectivity. It can also be used to correlate the residuals from any linear model, so that confounding effects such as time trends can be removed. A comparison with SVD approaches will be reported elsewhere.

The main drawbacks are computational effort, data storage, and display of high-dimensional data. At the moment, we have used large voxels (3 mm) to cut down computation time, and we only store correlations above a certain threshold, to cut down on storage. These are then displayed as arrows linking the 3D voxels that are significantly correlated. We also compute the 3D 'glass' correlation images, defined as

$$R_1^*(x_1, y_1, z_1) = \max_{x_2, y_2, z_2} R(x_1, y_1, z_1, x_2, y_2, z_2),$$

$$R_2^*(x_2, y_2, z_2) = \max_{x_1, y_1, z_1} R(x_1, y_1, z_1, x_2, y_2, z_2)$$

These are clearly identical for autocorrelation fields. Another drawback, which we are working on, is that the theoretical *P*-values are only accurate if the voxel size is small relative to the FWHM, otherwise a straightforward Bonferroni correction is better.

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