FMRI FUNCTIONAL CONNECTIVITY ESTIMATORS ROBUST TO REGION SIZE BIAS

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ABSTRACT

Analysis of interactions in the brain in terms of functional resting-state networks has yielded fundamental results in neuroscience. The first step in such analyses of functional connectivity typically involves computing correlations between brain regions. In this paper, we show theoretical results explaining why brain region sizes bias correlation estimators, and propose three new estimators to correct for region size influence. We show experimental results on both synthetic and real fMRI data and discuss the influence of noise and intra-regional correlation on the robustness of the estimators. The bootstrap-based estimator of correlations emerges as the preferred choice.

***Index Terms*—** correlation estimations, wavelets, fMRI brain connectivity

1. INTRODUCTION

The exploration of brain activity has gained great interest in recent years because of the non invasive techniques available to measure the functioning of the brain. Among them, Functional Magnetic Resonance Imaging (fMRI) allows to measure the change in blood flow related to neural activity. Resting state fMRI provides a technique to explore the brain at rest, without doing a given task. At rest, brain regions are organized like a network with a specific topology comprising hubs, and exhibits a modular organisation [1].

The definition of brain regions and evaluation of significant connections are challenging problems as fMRI data have a high anatomical resolution but low temporal resolution [2, 3]. Because of the large number of voxels acquired using fMRI, and the low signal to noise ratio at the voxel level, it is not practical to study the connectivity between all voxels. Two different approaches have been proposed, either using a smoothing technique for grouping the voxels [4], or defining an anatomical template to take the average of the voxels that belong to the same region [5, 6]. The second approach has the advantage of facilitating the representation of the connectivity networks using anatomical descriptions, and is simpler to use for the neuroscientist.

However it has been observed that the correlations computed by using regions with different sizes tend to be biased by the size of the regions [2, 3]. In this paper, we explain statistically that the measure of connection based on the correlation of the average voxels is biased by the number of voxels used in the average. On this basis, we propose a convergent estimator. We illustrate the efficiency of the new estimator on simulation of multivariate Gaussian variables. Finally, we illustrate the effect of this estimator on real data, and show that it is no longer biased by the size of the initially defined regions.

2. WAVELET CORRELATIONS FOR FMRI DATA

It has been shown that fMRI time series belong to the class of long memory processes [7]. A wavelet decomposition is therefore suitable to avoid bias due to the long dependence property of the time series. In [6], the authors used a wavelet correlation estimator to compute the connectivity networks for resting-state fMRI data. In this case, the correlation is estimated on the wavelet detail coefficients at each wavelet scale which corresponds to a frequency band. The estimator of wavelet correlation between two time series X and Y is given by,

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$$\hat{\rho}_{XY}(j) = \frac{\hat{\gamma}_{XY}(j)}{(\hat{\gamma}_X(j)\hat{\gamma}_Y(j))^{1/2}}$$

where $\hat{\gamma}_{XY}(j) = (1/n_j 2^j) \sum_k w_{j,k}^X w_{j,k}^Y$, n_j is the number of wavelet coefficients at scale j minus the number of boundary coefficients [8] and for k, $1 \leq k \leq n_j$, $w_{j,k}^X$ (resp. $w_{j,k}^Y$) are the wavelet coefficients at scale j for the time series X (resp. Y).

3. ESTIMATION OF CORRELATIONS : OBSERVATIONS AND OBJECTIVES

Based on an anatomical template with N anatomical regions, we extract the time series of each voxel belonging to a given region. That is for each region R_i, $1 \leq i \leq N$, we define a matrix $M_{R_i}, T \times N$ where T is the number of images acquired in the experiment, i.e. the length of the time series.For each region R_i, we extract,

$$M_{R_i} = \begin{bmatrix} X_{11} & X_{21} & \dots & X_{N_{R_i}1} \\ \vdots & \vdots & & \vdots \\ X_{1T} & X_{2T} & \dots & X_{N_{R_i}T} \end{bmatrix},$$

where N_{R_i} is the number of voxels contained in region R_i, and for j, $1 \leq j \leq N_{R_i}$, $X_{j1} \dots, X_{jT}$ is the time series associated to voxel j for region R_i.

In [6], the authors chose, for each region, to take the average of all the voxels at each time point. They obtain N time series, each associated to a region. Then, the computation of wavelet correlation was done on the average time series.

However, we observe that the *correlation between the average of time series* and the *average of correlations between all possible pairs of time series* are not equal. This was first reported in statistics, in the studies of familial data [9] where specific characteristics are obtained for different families with different sizes. In fMRI, Salvador *et al.* [2] also pointed out the link between value of correlation and size of the regions.

Figure 1 illustrates this fact on fMRI data : we used two different schemes to parcellate the original template into subregions. The spatial scheme consists in separating each region in two parts along the largest dimension. The random scheme consists in subdividing each region of the template by choosing the voxels in each subregion randomly, while keeping the number of voxels in each subregion as close as possible to the number of voxels in the spatial scheme. The first scheme will keep the connexity of each region, while the second has no constraints to that effect. In figure 1, we show that the random scheme will keep the center of gravity of each region and values of correlations very close to the original ones. However, the center of gravity of subdivided regions based on the spatial scheme will be different and we observe that the values of correlations are decreasing. This proves the existence of an intrinsic spatial structure in fMRI signals, which has to be taken into account in order to improve the estimation of correlations.

We will first illustrate this problem using a simple example, and then we will propose new estimators to correct this effect.

3.1. Model and definition of estimators

First, let us define the statistical hypotheses and quantities we want to analyse. In the sequel, ^{t} will denote the transpose of a vector or matrix.

Definition 3.1 *Let us define two random vectors :* $\mathbf{X} = (X_1, \dots, X_P)^t$ *and* $\mathbf{Y} = (Y_1, \dots, Y_M)^t$*, with a given inter-correlation structure, for all* i, j *such that* $1 \leq i \leq P$, $\quad 1 \leq j \leq M$*, we assume,* $cor(X_i, Y_j) = \eta_{X,Y}$*. In addition, let us note, for all* i*,* $1 \leq i \leq P, M$*,* $var(X_i) = \sigma_X^2$ *and* $var(Y_i) = \sigma_Y^2$*, and* $cor(X_i, X_j) = \rho_{i,j}^X$ *and* $cor(Y_i, Y_j) = \rho_{i,j}^Y$ *for* $1 \leq i, j \leq P (resp. M)$*. Without loss of generality, we will assume that* $\mathbf{X}$ *and* $\mathbf{Y}$ *have zero mean.*

Let us note $\mathbf{Z} = (\mathbf{X}^t, \ \mathbf{Y}^t)^t$*, and* $\mathbf{Z}_1, \dots, \mathbf{Z}_T$ *i.i.d. random vectors distributed as* $\mathbf{Z}$*.*

$$E(\mathbf{Z}\mathbf{Z}^t) = \begin{pmatrix} \Sigma_{XX} & \Sigma_{XY} \\ \Sigma_{YX} & \Sigma_{YY} \end{pmatrix}$$

is semi-positive definite.

The estimator of the correlation between $\bar{X}$ *and* $\bar{Y}$ *respectively average of* $X_1, \dots, X_P$ *and* $Y_1, \dots, Y_M$ *is defined as,*

$$\hat{\eta}_{\bar{X},\bar{Y}}^{agg} = \frac{\widehat{cov}(\bar{X}, \bar{Y})}{\hat{\sigma}_{\bar{X}} \hat{\sigma}_{\bar{Y}}}$$

where $\widehat{cov}$ *(resp.* $\hat{\sigma}$*) denotes the empirical estimator of covariance (resp. variance).*

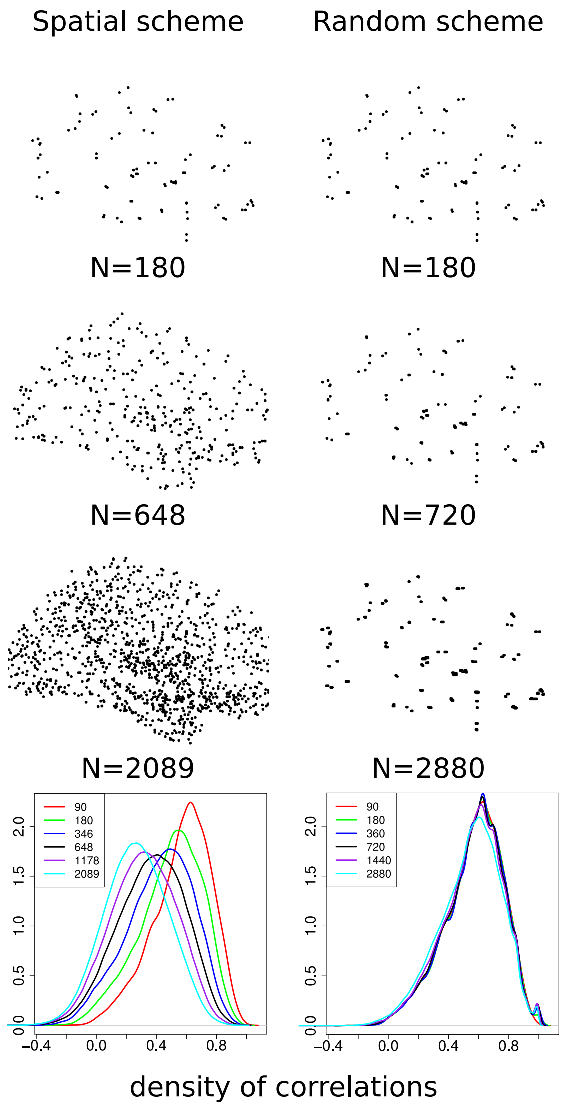

Fig. 1. Comparions of random and spatial scheme to down-sampling the regions of interest.

Proposition 3.1 *Under the hypotheses and notations of definition 3.1, the estimator* $\hat{\eta}^{agg}_{\bar{X},\bar{Y}}$ *is converging almost surely as* $T \to \infty$ *:*

$$\hat{\eta}^{agg}_{\bar{X},\bar{Y}} \overset{a.s.}{\to} PM \frac{\eta_{X,Y}}{\left(\sum_{i,j=1}^{P} \rho^X_{i,j}\right)^{1/2} \left(\sum_{i,j=1}^{M} \rho^Y_{i,j}\right)^{1/2}}$$

Remark 3.1 *From the proposition 3.1, we can deduce two simple cases,*

- *When* $\rho^X_{i,j} = \rho^Y_{i,j} = \delta_{i,j}$*, the limit is* $\sqrt{PM}\eta_{XY}$*.*
- *When* $\rho^X_{i,j} = \rho^Y_{i,j} = 1$*, the limit is equal to* η_{XY}*.*

Therefore, the size of the regions will have a greater impact when the voxels inside of the regions are independent.

Proposition 3.1 leads to the definition of three alternative estimators :

corrected estimator : the estimator corrected for the existence of intra-correlation.

$$\hat{\eta}^{agg,correct}_{\bar{X},\bar{Y}} = \frac{(\sum_{i,j=1}^{P} \hat{\rho}^X_{i,j} \sum_{i,j=1}^{M} \hat{\rho}^Y_{i,j})^{1/2}}{PM} \hat{\rho}_{\bar{X},\bar{Y}}. \quad (1)$$

average estimator : the estimator based on the average of all the possible correlations.

$$\hat{\eta}^{average}_{\bar{X},\bar{Y}} = \frac{1}{PM} \sum_{i=1}^{P} \sum_{j=1}^{M} \hat{\eta}_{X_i,Y_j}. \quad (2)$$

bootstrap estimator : the estimator based on the average of correlations computed from multiple random samplings. In order to take into account the spatial structure of fMRI data (voxels close in space will have high correlations), we propose to compute multiple estimations of correlation after taking the average of time series in several draws of randomly-placed small cubes of 64 mm^3 within each region. This has the advantage of decreasing the influence of noise at the voxel level. We denote this estimator $\hat{\eta}^{boot}$.

3.2. Results on simulated data

On the basis of the previous results, we simulated multivariate Gaussian distributions in order to compare the four estimators.

Figure 2 illustrates the efficiency of the estimators, with and without noise. We simulate two Gaussian vectors $\mathbf{X}$ and $\mathbf{Y}$ of size 21 and 70 respectively and inter-correlation equal to 0.2. For each vector, we simulate small cubes of 7 variables where the intra-correlation is close to 1. The structure of the matrix is illustrated in Figure 2. Based on this, we also tested the influence of noise by adding independent Gaussian noise to each variable.

These simulations show that all three estimators (corrected, average and bootstrap) are equivalent according to simulations without noise. However, the presence of noise has a crucial effect on the robustness of the corrected and average estimators. In taking into account the spatial structure, the bootstrap estimator seems more robust and more appropriate for real data.

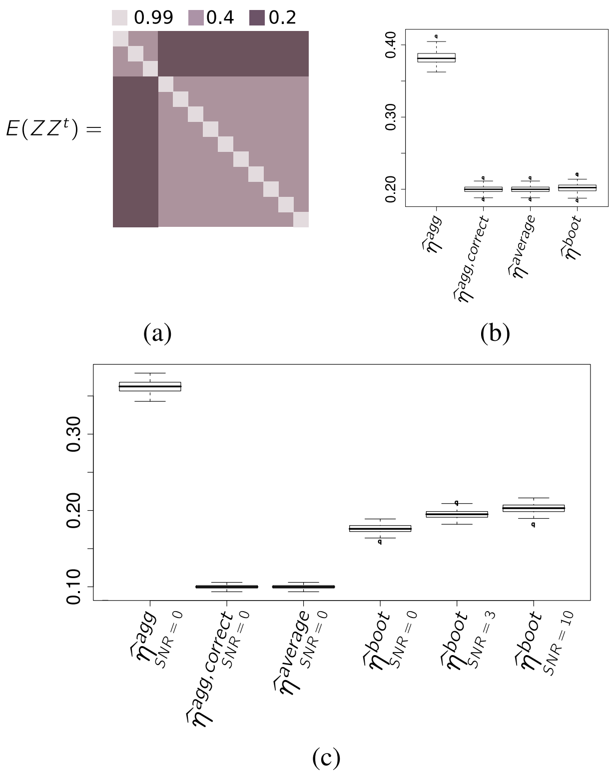

Fig. 2. Results on simulations of multivariate Gaussian distribution. (a) image of the covariance matrix used in simulations, with small cubes of 7 random variables with intra-correlation equal to 0.99. (b) results of estimations without noise. (c) results of estimations with different level of noise (10000 points in time and 100 repetitions of simulations).

4. REAL DATA

We tested the bootstrap estimator on resting-state fMRI data for 20 controls. Figure 3 illustrates the average correlations obtained with the aggregated and bootstrap estimators. The bootstrap estimator was computing on small cube of 64 mm^3, repeated 500 times. We can observe that using the bootstrap estimator, the smallest regions may have high correlations.

5. CONCLUSION

In this paper, we propose a new estimator of correlation to construct brain functional networks using anatomical template for the definition of regions. The introduced bootstrap estimator is adapted to the spatial structure of fMRI images and robust to noise. The use of this new estimator on real data leads to correct the effect of region size bias.

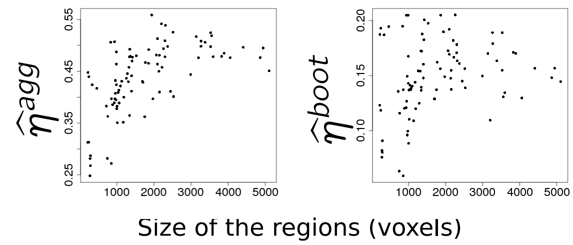

Fig. 3. Average correlations values obtained using 90 anatomical regions with the average (left) and bootstrap (right) estimators.

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